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TRANSMISSION OF POLIOMYELITIS VIRUS

ANALYSIS OF DIFFERING INTERPRETATIONS AND CONCEPTS PRACTICAL IMPLICATIONS

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PHYSICIANS and public health officers confronted with the question of how poliomyelitis is spread very often reply that "the exact method or methods of transmission of the disease are not known" and that "in the present state of our knowledge this cannot be answered."[1] When the confusion resulting from this "know-nothing" attitude nor the unconference to formulate some sort of statement about the mode of transmission, the following was said:

"Close association with infected persons accounts for the great majority of cases. Outbreaks attributable to milk have been rare and limited. Although flies have been found to be contaminated with virus, there has been no reliable evidence of spread by insects, water, food or sewage . . . Apparently the period of greatest communicability is covered by the latter part of the incubation period and the first week of the acute illness."[2]

It is my belief that neither the "know-nothing" attitude nor the unqualified statements just quoted are justifiable on the basis of available information.

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It is the purpose of this communication to analyze, on the one hand, "the present state of our knowledge" and, on the other, the differing interpretations, concepts, and practical implications resulting from it. Many epidemiologists have long held to the idea that the pattern of spread exhibited by poliomyelitis is best explained on the *hypothesis of respiratory transmission.*[3] In a recent popular article, it was stated: "It is commonly agreed that poliomyelitis is generally spread by contact between persons, in somewhat the same manner as diseases like measles and mumps are spread."[4] It need hardly be recalled here that the saliva is the main, and probably only, source of virus in mumps and that measles is associated with coryza and cough with the virus localized in the nasal mucosa and other portions of the respiratory tract. The epidemiological evidence generally given to support the hypothesis of respiratory transmission is as follows:

1. The rate of spread is rapid, i.e., an epidemic builds up rapidly and the number infected, including the minor illnesses and inapparent infections, is large.

2. The similarity to measles with regard to its tendency to radial spread,

i.e., "burning out" an involved area and extending into adjacent areas.

3. The demonstrated presence of the virus in the pharynx, or, as is frequently also stated, the nose and nasopharynx.

4. The conclusion gained from tracing contacts of patients, i.e., frank paralytic and nonparalytic patients who go to bed within a short time after onset, that the infectious period in poliomyelitis is brief (about five days before and five days after onset), corresponding more to the limited time the virus is demonstrable in the throat than to the longer time it is excreted in the stools. The natural corollary of this is that coughing, sneezing, and spitting out of material from the pharynx (nose, nasopharynx) in supplying droplets for transmission by the aerial route are somehow of special importance, since contamination of the hands, food, etc., is as prone to occur by virus eliminated in the feces as by that which is *assumed* to be eliminated with the respiratory secretions.

5. The fact that for many years the nasal route constituted almost the only natural portal by which monkeys could be infected with regularity, naturally led to the assumption that respiratory droplet infection was the most likely way for the virus to obtain entrance to the nasal mucosa. After it was demonstrated that infection by the nasal route in experimental animals invariably affects the olfactory pathway, and when it was found that in human beings the olfactory pathway is not involved, it was assumed by some that in human beings the respiratory, rather that the olfactory, nasal mucosa, and the nasopharynx served as the sites of entry, multiplication, and exit of the virus.

It is perhaps an established epidemiological principle that epidemiological probability must be compatible with bacteriologic (or virologic) possibility, particularly when the epidemiological probabilities lend themselves to several alternative explanations. It is of primary importance, therefore, to establish the facts regarding the available sources of poliomyelitis virus and the potential routes by which infection may be transmitted. The bulk of our knowledge regarding the sources of poliomyelitis virus in nature has been accumulated between 1938 and 1946, and no significant new information has been brought forward in the past five years.[5] The systematic studies on the location of the virus in the human body, both in patients dying shortly after onset of illness as well as during life, analyzed in recent publications,[5] indicated that the alimentary tract is the one system, outside of the central nervous system, in which virus was regularly found. There is no disagreement among poliomyelitis investigators regarding the presence of poliomyelitis virus in the *oropharynx* (rather than nasopharynx) early after infection, although the frequency of positive isolations from throat swabs has varied from a high of 43 per cent in the first three days of illness[6] to a low of 11 per cent during the first week of illness.[7] Studies on fatal cases indicated that, in any one patient, the virus may or may not be found in the washed tissues of the oropharynx, although it is invariably found at one or another level of the alimentary tract.[8] It is now well established that virus can be detected in the stools with a frequency ranging from 70 to 90 per cent during the first week of illness, and about 50 per cent in the third and fourth weeks after onset, not only in frank cases of the disease, but also in children with the subclinical or very minor illness type of infection.[9, 9a]

The statement is frequently made that the virus is present in the nose

or nasopharynx, but critical analysis of the data reveals that it is entirely without foundation. The occasional positive tests obtained years ago with so-called "nasopharyngeal secretions or washings" which, because of the method used, also contained material from the oropharynx cannot be evaluated. It is noteworthy, however, that Kessel, Moore, Stimpert, and Fisk[10] reported only negative results in tests on "nasal washings" from 139 patients. Ward and I[11] tested the entire nasal mucosa (and not the olfactory mucosa only, as was wrongly quoted by Howe[12]) of patients dying within a few days after onset of illness and found the virus in none, although it was recovered from the oropharynx or other parts of the alimentary tract. We also collected nasal secretions only, on multiple cotton plugs inserted deep in the nose for a period of three days, from twenty-two paralytic patients and obtained completely negative results, even when the collections were started as early as three days after onset of first symptoms; a single stool specimen or enema obtained at the termination of this three-day period yielded virus in ten of these patients. It should be noted here that similar negative results were obtained with the saliva expectorated naturally over a period of three days without hawking or coughing by twenty of this same group of patients. The salivary glands from fatal cases were also devoid of virus. Ward and Walters,[13] in a later study on nineteen patients, all within four days after onset of symptoms, swabbed the nose and throat separately after, however, the patient had been made to cough, blow, expectorate, and talk for one-half hour into sterile gauze masks which were tied over the mouth and nose. While the throat swabs yielded virus in six of the nineteen patients, the nose swabs were negative in eighteen, the only positive being in a patient whose wet mask also yielded the virus. It is thus clear that in five patients who had demonstrable virus in the oropharynx, none was found in the nose. This indicates that the absence of virus isolations from the nose of patients cannot be attributed to antibody in the secretions, since, if sufficient homologous antibody were present in the nasopharyngeal secretions so early after onset, it should also preclude detection of the virus in the pharynx.

For practical purposes, the discussion as to whether the virus is present only in the oropharynx or in the nose as well may at first glance appear to be academic, were it not for the demonstration that pathogens in the upper respiratory tract are eliminated differently, i.e., by different types of activities, when they are present only in the throat, from when they are present in both nose and throat. Hamburger and his associates[14] in a series of striking studies on the dissemination of beta hemolytic streptococci and the conditions which predispose to outbreaks clearly showed that the "dangerous" carrier both as regards dissemination by droplets or by hands is the individual with organisms in the nose as well as his throat, while the one who carries the organisms only in his throat is relatively harmless. Since it is reasonable to suppose that poliomyelitis virus as well as hemolytic streptococci are emitted on carrier particles and not in the "naked" state, the mechanisms of dissemination from the throat unquestionably apply to both. Therefore, the presence or absence of

poliomyelitis virus in the nose assumes more than academic interest. If we eliminate the nasal secretions from consideration, as I believe the evidence warrants, can we then say that poliomyelitis virus in the oropharynx is ordinarily expelled in the form of droplets by mouth spray as a result of the normal activities of either the asymptomatic or ill carrier? The patient with poliomyelitis does not have the cough and coryza, characteristic of measles. We may recall again that in the tests on nineteen patients who were *made* to cough and hawk into sterile gauze masks for one-half hour, only two yielded virus on the masks, and that the saliva collected over a period of three days from another group of twenty patients, without coughing or hawking, yielded no virus. If the saliva, as it is normally expectorated, rarely, if ever, contains the virus in amounts comparable to that readily recovered from the stools, have we any basis for regarding pharyngeal secretions either as a source of droplets for aerial transmission of infection or as a significant source of virus for contamination of the hands? For, if we leave out the droplets from consideration, upon which the hypothesis of respiratory transmission rests so heavily for its explanation of rapid and extensive spread, and consider only the contamination of hands and other objects, which may enter the mouth, the demonstrated abundance of virus in the feces offers much greater opportunities for that type of contamination. Thus, it would appear that those who interpret the available data as favoring the idea that poliomyelitis is predominantly transmitted through pharyngeal secretions cannot continue to uphold this concept as long as the available evidence indicates that the oropharynx, under ordinary circumstances, cannot be a significant source of virus-laden droplets for the outer environment. It is also inconceivable that the aspiration of droplet nuclei, on their way to the pharynx via the nose, would fail to involve the olfactory mucosa which offers such an excellent portal of entry for poliomyelitis virus in all other hosts. If the present data are accepted, the respiratory transmission hypothesis loses its virologic support. Since the practical implications of either accepting or discarding the respiratory transmission hypothesis are of considerable significance to public health practice, additional studies on the droplet-generating capacities of the oropharynx and infectivity of saliva and mouth spray are indicated to settle this matter once and for all.

If, for want of evidence, we discard the assumption that pharyngeal secretions are of importance in the ordinary* spread of poliomyelitis virus, the epidemiological observations pointing to the importance of intimate, rather than casual, association lose none of their significance. As a matter of fact, when epidemiologists call upon respiratory transmission to account for the rapid spread observed in many poliomyelitis outbreaks, they have to postulate transmission by casual association resulting from exposure to virus-laden droplets rather than the intimate association which appears to be important in poliomyelitis. Virus eliminated in the stools can be as effectively spread by intimate association as by a number of

*This is to stress that the pharyngeal secretions of a patient with bulbar poliomyelitis can be an important source of infection for a nurse aspirating such secretions.

other potential modes of dissemination. If the introduction of the virus into the mouth by means of the hands or other materials is of basic importance in the transmission of poliomyelitis, can we regard the period of communicability as being for only a few days before and a few days to a week after onset of symptoms, when, by our present methods, the virus is still readily demonstrable in the stools of approximately 50 per cent of individuals during the third and fourth weeks? How much reliance should we place on the epidemiological observations which place the "infectious period" at four to five days before and after onset of symptoms, when it is realized that these conclusions are based on tracing extrafamilial secondary cases to presumably single contacts with patients who became sick and had to go to bed? These frank cases are generally removed from further contact with others, except for a limited number of adults who care for them in hospitals—and the occurrence of paralytic poliomyelitis among nurses caring for such patients, while uncommon, is not rare. The recent reports on poliomyelitis among isolated groups of Eskimos in the Canadian Arctic contains a possible instance of transmission of infection by a recovered patient with residual paralysis, which is worth quoting: "Between December 5 and 15 one of the Eskimo Point cases who had residual paralysis of the shoulder girdle visited all the camps in the Padlei areas (125 miles inland). About 2 weeks after his departure from the district, cases began to appear. In a group of 50 natives there were 2 deaths and 10 cases of paralysis."[15] Since there is good reason to believe that the asymptomatic and subclinically infected carriers, who are not confined to bed and cannot, as yet, be identified, outnumber the frank cases, the period of communicability of infection from the frank cases is of special importance to nurses, physiotherapists, and physicians who have to care for them. In my opinion, it is not justifiable to tell these people that the period of communicability is brief, because the available data do not permit us to say that it is brief. We should rather guide ourselves by the known facts regarding the incidence of virus in the stools at various times after onset. We have no right to convey the impression that the virus which the patient is putting out in his stools two to three weeks after onset is of no importance in spreading infection. While it is possible that the quantity of virus in the stool may, as a rule, be greater during the first week after onset and, accordingly, may give rise to more clinically apparent cases, there is at present no information one way or another on this point. Apropos of this, there is an interesting report of an outbreak of several cases of poliomyelitis in the family of an American physician in the Philippines who was in charge of all the poliomyelitis patients during a local outbreak and who, himself, remained well.[16]

Before proceeding further with the analysis of the role and consequences of fecal transmission in poliomyelitis, it is perhaps necessary to recall that the possibility of infection by the oral route has been established beyond doubt, especially in cynomolgus monkeys and in chimpanzees. It is especially by this route of virus administration that it has been possible to reproduce the whole spectrum of

the consequences of poliomyelitis infection seen in man, namely, paralytic, nonparalytic, and inapparent, the last without histologic evidence of involvement of the nervous system but associated with the development of specific antibodies. The oral route of infection is now commonly used by investigators who wish to imitate the conditions that may obtain in man. It is especially pertinent, therefore, to examine the statement that there is no "crucial evidence" concerning the role of fecal contamination in the transmission of poliomyelitis, because it is implied that epidemics traceable to contaminated food or water supplies are unknown. As regards the principle of virologic possibility, the evidence is ample for the role of fecal contamination and grossly deficient or absent for any other mode of transmission. The three examples of minor outbreaks conceivably attributable to the consumption of raw, infected milk, which are usually cited as the exceptions, are not the only instances of explosive outbreaks occurring under circumstances suggesting a common source in infected food or drink. Two, possibly food-borne, outbreaks were reported among military personnel in the United States,[17, 18] and a recent analysis of the Army experience revealed two more explosive outbreaks of a similar nature in the United States, and at least one in the Philippines for the period ending in 1945.[19] McAlpine[20] reported an explosive outbreak affecting eight British officers who had stayed at a hotel in India. He, furthermore, brought forth suggestive evidence that the five times higher incidence of poliomyelitis among British officers, as compared with other ranks in India, may be attributed to the lower standard of hygiene in officers' messes and their greater use of civilian-controlled establishments. In 1946, I had an opportunity to observe an explosive outbreak of poliomyelitis among U. S. Marines stationed in Tientsin, which suggested primary infection from a common source over a limited period of time. The experience of the American Army during World War II also showed that the markedly increased poliomyelitis incidence occurred in those parts of the world where other enteric infections and infectious hepatitis were also high, while the rates among the Armed Forces in the United States and Europe were as low as those for civilians of the same age group.[19]

It seems to me important to stress that one cannot apply "unitarian" epidemiological hypotheses or concepts in dealing with an infectious agent that is predominantly stool-borne. One method of dissemination may predominate under one set of circumstances, and other methods or varying combinations of them under other circumstances. When several alternative explanations may apply equally well, one cannot speak of "crucial evidence" for any one. In the case of poliomyelitis virus one could hardly expect to trace a whole epidemic to consumption of any one particular article of food. One must visualize rather the possibility of isolated carriers (not necessarily human) depositing virus on a variety of articles which are ordinarily consumed uncooked. If one grants that infection can be transmitted by putting contaminated fingers into the mouth, one cannot possibly deny that contaminated food or drink may accomplish the same effect. When one considers that on occasion

only one out of ten or one out of 100 may become a clinically recognized or suspect case of infection, it is not surprising that more isolated instances, which can be interpreted as strictly food-borne outbreaks, are not available. Actually, one of the most striking facts in the epidemiology of poliomyelitis is the regularity with which most members of a family either succumb within a few days of one another when there are multiple frank cases,[21] or are found to be simultaneous carriers of the virus.[22] While there are a number of possible explanations for this, all of which may apply at different times, the consumption of a common article of food or drink, contaminated before or after it reaches the home, is as plausible and possible as any other. The fact that there are no water-borne epidemics on record merely indicates that, aside from dilution, the ordinary methods of water purification may help to rid sewage-polluted water of all or most of the virus. It does not mean, however, that, if virus were present in water in adequate concentration, it could not produce infection. The recent demonstration by Wenner and Branson[23] of poliomyelitis virus in creek water indicates that drainage from privies can, under certain circumstances, contaminate a water supply.

Similarly, while the purified, city water which *enters* a public swimming pool may be regarded as being devoid of poliomyelitis virus, there are good possibilities for contamination with oropharyngeal and anal washings, which may be limited as to place and time, when large numbers of people use it during an outbreak of the disease. During an investigation of an epidemic of poliomyelitis in Berlin, Germany, in 1947, I found that within one week eighteen of approximately 150 children, who played in a shallow, concrete wading pool, developed poliomyelitis.[24] These were among the first cases of this epidemic and during the same period only nine other cases occurred scattered among the remainder of the Berlin population.

In a discussion of all these factors one inevitably must consider the role of filth flies in poliomyelitis just as one does in dysentery and other stool-borne infections. The present state of our knowledge with regard to poliomyelitis and filth flies is as follows:

1. The virus has been repeatedly demonstrated in flies in both rural and urban communities during outbreaks of poliomyelitis.

2. Laboratory-reared flies, artificially infected with poliomyelitis virus contained in human stool, excreted virus for as long as twenty-one days under conditions which raised the question of possible multiplication in the fly.[25]

3. Food exposed to flies in an epidemic area was contaminated with enough virus to produce infection in chimpanzees which ate it.[26]

4. The filth flies under consideration, such as the green-bottle fly (*Phaenicia sericata*) and the blow fly (*Phormia regina*), are attracted to human feces and to common foods.

The problem as regards the role of flies in poliomyelitis is not whether or not the infection can be transmitted without them, and not whether or not outbreaks can occur without them, because it is established, as in the case of dysentery, that flies are not necessary to account for either. However, to say that flies are not necessary to account for transmission under one set of circumstances is not the same as to say that they are incapable of trans-

mission or that at certain times of the year in certain places under special circumstances, their role as accessory agents of transmission may not be important. One of the important unsolved problems in poliomyelitis is why in temperate zones approximately 80 to 90 per cent of the cases occur during four months of the year in late summer and early autumn. Of course, dissemination of fecal material during warm weather may be facilitated by agencies other than flies. The fewer and lighter clothes that children and adults wear during the summer make it a great deal easier to get their hands contaminated in hot weather than it does in cold weather. The assumption that some physiologic change in the host is responsible receives little support from the occurrence of winter epidemics or from the fact that when an epidemic starts late in the summer or early autumn it can continue for several months after the advent of cold weather. The latter observation also makes it quite clear that whether or not flies, by serving as additional nonhuman carriers, may play an important role in the primary initiation of an epidemic, the large number of human carriers who have become seeded with virus by the time a large urban epidemic has reached its peak is unquestionably itself capable of maintaining dissemination on a large scale. This, and not the few inconclusive DDT tests, is the real basis for the general agreement that there is no justification for initiating *emergency* community insect control measures in the hope of influencing an *established* epidemic of poliomyelitis. But this should not be interpreted that measures designed to minimize contamination of food by flies, whether in stores, markets, or homes, should not be encouraged.

In my opinion, the filth fly must be regarded in the same light as the human carrier during poliomyelitis epidemics. The possibility remains that the rapid peak reached by certain large urban epidemics, in contradistinction to localized outbreaks, may be the result of the more widespread dissemination of virus by myriads of contaminated flies. It is not true, as some would have it, that the replacement of the horse by the automobile has led to the disappearance of the flies (we are not concerned with the biting flies), for we have had no difficulty in collecting pounds of flies in properly baited traps in the most modern American cities during poliomyelitis epidemics.[8, 27, 28]

In 1947 I had an opportunity to study the first large epidemic of poliomyelitis in Berlin, Germany. Because of an unexpected outbreak of malaria the preceding year, it so happened that *just before* the beginning of the 1947 poliomyelitis epidemic was suspected, somewhat more than one-half of the city was sprayed with DDT from the air and from the ground, and the remainder was not so treated because the U. S. S. R. authorities refused to go along with this plan. There were at that time no obstacles to movement of population between the different sectors, and the number of reported poliomyelitis cases in the preceding months of the year was small and about the same in all sectors. Two months after the single spraying of DDT, the poliomyelitis attack rate was twice as high in the untreated Russian sector as in the remainder of Berlin, that is 65 per 100,000 as compared with 32 per 100,000. By the end of the year the attack

rate was 103 per 100,000 in the Russian sector as compared with 61 per 100,000 in the remainder of Berlin.[24] It is doubtful how soon, if ever, such an experiment may be carried out again in a large metropolis, and it is at least worth keeping it in mind in considering the potential role of flies in the initial stages of a poliomyelitis epidemic. This is not to say that under different circumstances there may not be as much poliomyelitis without flies as with flies.

From the point of view of public health practice, it is of considerable importance which of the various views that I have analyzed are closest to the truth. For, according to the respiratory hypothesis, you can get the infection without touching anything or anybody or swallowing anything, and the epidemiological prototype for poliomyelitis is measles or influenza. If one follows this hypothesis to its logical conclusion, the greatest danger of acquiring the infection would be in places where large numbers of people are congregated and not necessarily as a result of "intimate association." It would also follow that admission of patients on general hospital wards would be contraindicated and the attendance of children at schools during an epidemic would be fraught with special danger. And, yet, it is probably widely agreed, even by the adherents of the respiratory hypothesis, that attendance at school, admission of patients on open wards, and attendance at large gatherings, such as movies and churches, are not fraught with special danger. Both in Berlin in 1947[29] and in New York City in 1949,[30] it has been observed that attendance at school during an epidemic failed to alter the incidence of the disease in the very age group which has the highest susceptibility. On the other hand, if one grants that fecal contamination constitutes the most important factor in transmission, it is clear that ordinarily you cannot get the infection without touching somebody or something contaminated with virus and transferring it with the fingers to the mouth or swallowing food which has been contaminated in any of a great variety of ways, and the most likely epidemiological prototype for poliomyelitis becomes bacillary dysentery. It is also clear that under different circumstances and conditions, the various potential modes of transmission may assume special significance.

While the ratio of inapparent to clinically recognized cases may vary in different types of outbreaks, a number of studies have indicated that the incidence of silent infections among *noncontacts* may vary from 1 to 10 per cent in the child population[9a] and probably less in the adult population. If by the time a given epidemic is recognized as many as 10 per cent of the children in the community are already silent carriers of the virus, it is clear why measures directed only against the recognized cases, their family associates or other agencies of viral dissemination will not succeed in stopping the epidemic. Is it fair, however, to imply that, because certain measures cannot be expected to stop an epidemic, no measures at all should be taken to protect oneself against potential sources of infection, either known or probable?

The fundamental concept that "any measure that stops or significantly decreases the spread of an infectious agent without building up immunity in the general population may do noth-

ing more than postpone the appearance of an epidemic and set the stage for a devastating outbreak which would find so many more people without resistance when the infectious agent finally was introduced again into the community''[31] should not, in my opinion, be used to discourage the observance of certain measures during *epidemics* of poliomyelitis.

Epidemiological data, particularly those dealing with the age distribution of recognized cases during epidemics which occur after a varying number of years of relatively low incidence, have long ago led to the conclusion that subclinical immunization occurs not only during epidemic periods but during interepidemic years as well.[29, 32] There is, furthermore, both epidemiological and laboratory evidence[9a, 33, 34] that the virulence of some strains of poliomyelitis virus is greater than that of others and may constitute one of the factors which determines the severity of the disease. It is not unlikely that at least one of the important factors determining the occurrence of an epidemic or severe outbreak is the special virulence of the strain of virus which is being disseminated in a community. Accordingly, it seems to me that the observance of certain elementary rules of hygiene which are calculated to diminish the chances of stool-borne virus are to be encouraged rather than discouraged during epidemics of poliomyelitis.

CONCLUSIONS

1. The present state of our knowledge concerning the sources of poliomyelitis virus in nature permits a rational approach to a consideration of its transmission.

2. Statements by public health officers that ''poliomyelitis contagion is a mystery,'' or that ''the exact method or methods of transmission are unknown'' are unjustifiable and contribute to poor morale and public hysteria.

3. Available knowledge justifies the conclusion that human feces derived from patients and healthy carriers is the most significant source of virus in nature. Available evidence indicates that the virus which is occasionally present in the throat of patients and healthy carriers does not *ordinarily* reach the outer environment in significant amounts by droplets from the mouth or nose. To remove this conclusion from the field of controversy, it is suggested that additional studies be carried out on the infectivity of *naturally* expectorated saliva and *naturally* emitted mouth spray derived from patients, in the earliest stages of the disease, and from their familial associates.

4. The period of communicability cannot at present be said to be limited to a few days before and a few days after onset of illness, but should rather be regarded as potential during the period that virus is generally eliminated in the feces. While it is possible that the period of communicability *may be* greatest during the few days before and the week after onset, because the amount of virus eliminated in the feces during that period *may be* greatest, there is no specific quantitative information on this point. Since there is, as yet, no simple laboratory test for the virus, which can be used on individual patients, one may use as a guide the fact that approximately 50 per cent of patients still have demon-

strable virus in their stools three to four weeks after onset.

5. It is not justifiable to stress one method whereby stool-borne virus may be transmitted and to minimize others, because the relative importance of any one method can vary with the circumstances.

6. Excepting artificial conditions, entry of poliomyelitis virus by way of the mouth can be justifiably regarded as the usual mode of infection. Accordingly, it follows that contaminated food and drink are as important as contaminated fingers in introducing the virus into the body. This does not mean that any single food or drink is of importance but rather that under different circumstances, within the confines of a family, a mess, a store, a portion of a community, etc., some food or drink may be contaminated by a human or nonhuman carrier of the virus, and, when consumed uncooked, can become the source of infection.

7. Under certain conditions, in urban as well as rural communities, filth flies as well as human beings can be carriers of poliomyelitis virus, and should be regarded in the same light. The incidence of infection naturally varies in both. In some limited outbreaks, the familial associates of recognized cases are most important as carriers, while in large metropolitan, urban epidemics, the cases and carriers are widely scattered throughout the city. By the time the existence of an epidemic is recognized in a large city, there are usually already so many healthy human carriers involved in the dissemination of the virus that neither complete isolation of patients and their associates nor the destruction of the filth-fly carriers can be expected to stop an epidemic. This is the real basis for the general agreement that there is no justification for initiating *emergency* insect control measures in the hope of stopping a poliomyelitis epidemic. However, individual measures designed to combat filth flies and to minimize contamination of food by flies in markets or homes should receive the same encouragement as the observance of other hygienic measures which are designed to diminish the chances of infection for the individual, without any guarantee of absolute personal protection or promise of stopping the epidemic. The most important point to realize is that many methods of transmission are involved in a large outbreak of poliomyelitis, and that no single measure can be relied upon for crucial effectiveness.

8. Subclinical immunization occurs during nonepidemic years as well as during epidemics, and there is reason to believe that strains of greater virulence are in circulation in a community during an epidemic period. Accordingly, it is not justifiable to object to measures designed to diminish the individual's chances of infection during an epidemic on the grounds that it would only delay to a less favorable age the natural immunization process.

9. While the existence of large numbers of unrecognizable healthy human carriers imposes an insuperable obstacle in the control of a large epidemic, it is not, in my opinion, sound practice to disregard the known potential infectiousness of the recognizable and suspected cases and their familial or other intimate associates. Accordingly, it seems unwise to deprecate the advisability of modified isolation procedures for these individuals in an attempt to lessen their opportunities for infecting others with

whom they might come into intimate association or whose food they might contaminate.

10. Since there is no evidence for the transmission of poliomyelitis by droplet nuclei, the following measures which are sometimes advocated during poliomyelitis epidemics are *not* warranted:

(a) Avoidance of crowds, large public gatherings or sports events.

(b) Exclusion of children under 16 years of age from movies, churches, or schools.

(c) Exclusion of poliomyelitis patients and suspects from general hospital wards.

11. On the other hand, it appears reasonable during *epidemic periods* for *individuals* to take the following simple steps to diminish the risks of acquiring infection:

(a) Keep fingers out of mouth and wash hands before eating.

(b) Keep flies away from all food, and thoroughly wash that which is consumed uncooked, e.g., vegetables, fruit, etc.

(c) Keep children under 16 out of crowded, public wading and swimming pools.

(d) Avoid *intimate* association (shaking hands, kissing, common eating utensils, towels, etc.) with members of a family in which a case of poliomyelitis has occurred within three weeks, even though the patient has been removed to a hospital.

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VARIOUS ASPECTS OF ADOLESCENCE

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THOSE few physicians who confine their attention to adolescents are not infrequently asked in what manner and to what degree the health problems of that age group differ from those of a child or from those of an adult. Adolescents do present problems peculiar to their age, but they are not grave ones and they do not require the creation of another specialty. The proper care of adolescents requires only that the family physician, the pediatrician, parents and teachers treat these young people as adolescents, not as little children, not as adults; they are not little boys or little girls any more, and they are not adults yet: they are young people who are beginning to be adults. When this simple fact is really understood, many of the matters peculiar to adolescence will no longer appear to be problems; until it is, the adolescent will continue to seem to many to be an enigma.

If any one specialty were to take over the care of adolescents, it should be pediatrics. The problems of growth, the contagious diseases, the behavior problems, and the blood and bone disorders which the pediatrician cares for in childhood should be observed and treated by him until his patient becomes an adult. Too often such a patient is abandoned just because he is fourteen: that would seem an inadequate reason for changing from the doctor who for many years had cared for the results of poliomyelitis, retarded growth, friction with parents, or asthma. Those, by and large, are not problems of adulthood—they will have been straightened out by the time the growth process is over. Until that time it would seem best for the patient to be retained by the physician who cared for those ailments from their beginning.

There is no better way both to explain and to reiterate the necessity of interpreting and handling these young people in terms of the age group to which they belong than to discuss a few of the conditions which are not only common in them but which also are of particular significance *to* them. The limitations of this writer's experience is the only excuse for confining these remarks to the male adolescent; the female at this age is just as worthy of special consideration.

GROWTH AND DEVELOPMENT

A study of the growth and development phenomena of adolescents furnishes an excellent means of understanding the problems peculiar to

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them. These are matters which deeply concern them. The small child or the 30-year-old adult cares little about his height or state of maturity, but the 15-year-old wants to know how tall he will be, when he will thin out, and when his beard will appear.

Parents and teachers as well as the adolescent himself need to know something about growth in this age group. They find it difficult to understand that there is nothing orderly about growth, that there is no one best way of growing, that there is neither an ideal type of behavior nor an ideal size at any given age. The boy who is tall and heavy and bearded at 14 is expected to "act like a man" and yet if he asks for the privileges which his slight and beardless 17-year-old brother has been granted, he is firmly reminded of his age. All this confusion can be avoided if one will regard chronological age with some suspicion during the adolescent years. These young people vary too much in the rate and manner in which they grow and mature to make chronological age a good yardstick.[12]

The evaluation of the hand-wrist x-ray provides a skeletal age[13] which is a more suitable index of the adolescent's growth and maturity status than is the figure based upon his birth date. Hand-wrist x-rays of two boys both 14 years 11 months of age are shown in Fig. 1. In contrast to their similar chronological ages, their skeletal ages are forty months apart. These were both normal healthy boys. They differed in a natural way in their rate of growth, but there is no reason to suspect that each was not growing properly, that one will not mature, or that the other has grown too fast.

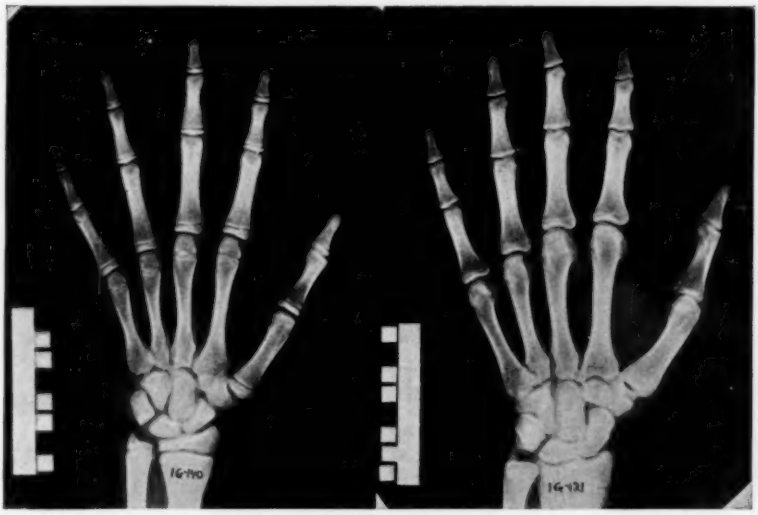


Fig. 1.—Hand-wrist x-rays of two boys, each of whose chronological age was 14 years 11 months. Evaluation of these films yielded a skeletal age rating of 13 years 6 months for the x-ray at the left (IG-140) and of 16 years 10 months for that at the right (IG-121).

The variation in state of maturity which one finds at any given age during adolescence is also illustrated in Fig. 2. Degree of maturity,[11] based on the status of secondary sex characteristics, can be rated objectively and will be found to parallel closely the skeletal age ratings. The six boys in Fig. 2 were all 14 years 9 months of age. They have been arranged in order of ascending skeletal age (based on their hand-wrist x-rays): these skeletal ages ranged from 13 years 2 months (nineteen months below his chronological age) to 17 years 3 months (thirty months above his chronological age). Their maturation ratings[11] ranged from three to five.

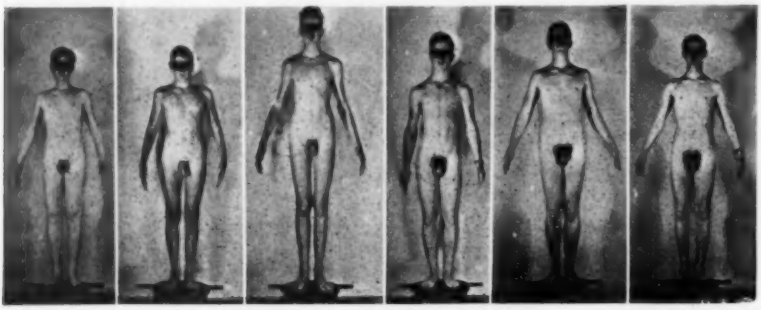


Fig. 2.—Each of these six boys was photographed when his chronological age was 14 years 9 month. Their skeletal ages, however, were (from left to right) 13 years 2 months, 14 years 1 month, 14 years 9 months, 15 years 7 months, 15 years 11 months, and 17 years 3 months. Their maturation rating were 3, 3-4, 4, 4-5, 5, and 5.

The facts which parents and teachers and the boys themselves need thoroughly to understand is that among perfectly normal adolescents there is great variation in size and in state of maturity, that there is no one way of growing which is better than another, that true abnormalities in growth are extremely rare.[5] To expect the boy at the left in Fig. 2 to behave in the same manner as the boy at the right, to treat him in the same manner, to hold him to the same duties, studies, and responsibilities is neither entirely logical nor always successful.

That real abnormalities are rare, that almost every child will eventually grow and mature is hard for both parent and child to understand: they desire that what they consider a standard average pattern be followed. It will help to explain patiently that each will, and is entitled to, grow in his own way. That these ways differ, but that as long as there is no true abnormality and as long as there is some evidence of progress no matter how slight, all will be well, is shown in Figs. 3*A* and 3*B*. Fig. 3*A* shows three boys whose chronological ages were 14 years 7 months, 15 years 5 months, and 14 years 9 months, whose maturation ratings were 3, 4-5, and 5, whose skeletal ages were 13 years 6 months, 15 years 3 months, and 15 years 8 months. In Fig. 3*B* these same boys are shown eight years later; at that time there obviously was no appreciable difference in their maturity, masculinity, or size.

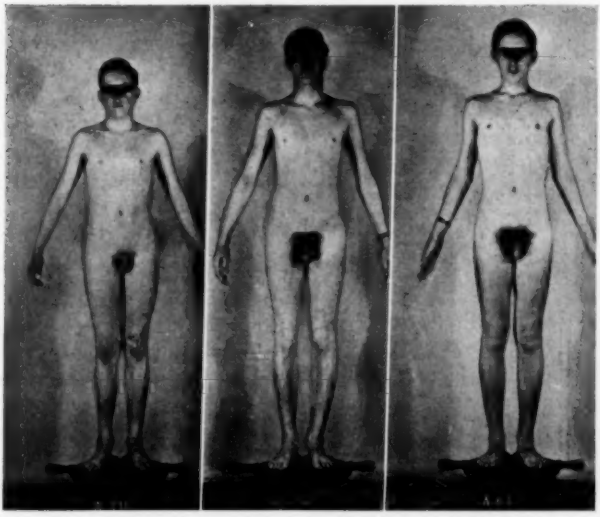


Fig. 3*A*.—Three boys photographed when their chronological ages were 14 years 7 months, 15 years 5 months, and 14 years 9 months. The skeletal ages at that time was 13 years 6 months, 15 years 3 months, and 15 years 8 months; and their maturation ratings were 3, 4-5, and 5.

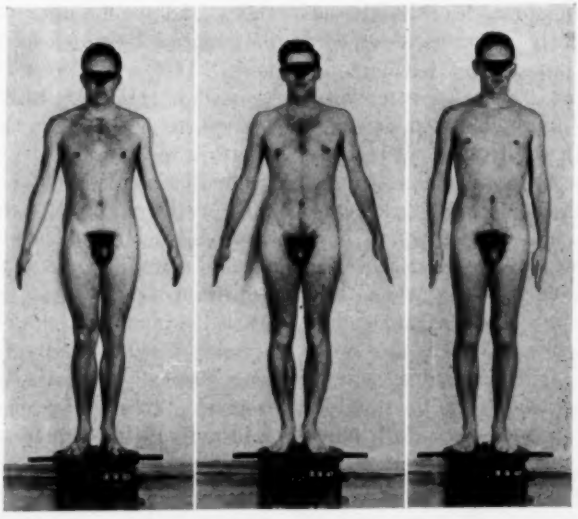


Fig. 3*B*.—The boys shown in Fig. 3*A* were again photographed eight years later. The rates at which these three boys matured were very different, but the end results were similar.

INFECTIOUS DISEASES

In connection with infectious diseases during adolescence it is important to remember that members of this age group may have lost the benefits of the immunizations which were given them in early childhood. It is common practice nowadays to vaccinate against smallpox and to give toxoids to immunize against tetanus and diphtheria during the first year. Adolescents are, in general, a healthy group: many of them rarely go to a doctor and it is easy to overlook the renewal of their immunity against these particular diseases. The adolescent who has not been vaccinated or who has not been immunized against diphtheria[18] or tetanus for several years certainly requires that these procedures be repeated.

The tendency to protect young children from mumps, measles, chicken pox, and German measles is ill-advised. Mothers, overly apprehensive concerning all illness, and teachers too conscious of school attendance records, often try to avoid exposing children to these diseases. It is never convenient to have mumps or German measles,[6] but it is better preventive medicine to allow children to have these and other contagious diseases during their early years when these ailments are often less severe and of less consequence. There is also much to be said for encouraging parents and teachers to accept these minor illnesses as a necessary evil, more appropriate to childhood than to later life, and definitely not as a proper source of anxiety. Rumors about an epidemic, a frantic searching for and isolation of contacts the moment a case of chicken pox appears in the fourth grade is poor health education and worse mental hygiene. The only proper method of controlling these illnesses among healthy children in adolescence (except for the use of gamma globulin for measles modification[15]) is to urge that they have them while they are still little children.

HEALTH EDUCATION

Physicians are not infrequently asked to serve upon school boards and may well be asked what constitutes proper subject matter for a health education course. It seems fair to say that the attitude which a boy has toward his health is the most important part of his health education. The avoidance of anxiety toward illness and the avoidance of the pill habit should start in infancy but they will need reinforcement as the boy gets older and is subjected to fear advertising, his playmates' habits and attitudes, and the peculiar ways of some of those adults whom he learns to admire. If the adolescent has not developed a rational, objective attitude toward his health, it is not too late to try to give him one. To interest him in finding causes rather than taking pills, to help him to avoid worrying about his health and from being reckless is more important than that he acquire a smattering of physiology or learn the incubation period of measles.

Some factual information,[3] as well as a basically sound attitude, is important. The fat boy or the thin boy is usually willing to learn something about nutrition. Ways to avoid accidents are, for this age group, the most valuable of all health education subjects. Most of them want to know something about acne, whether strenuous exercise or smoking is

harmful, how much sleep they should have. Sex education has real meaning for them.

A good many have questions about growth and development: a boy such as the one at the left in Fig. 3*A* needs to be told a good deal about the way in which young people's growth varies one from the other. This boy, who was a little less than 62 inches tall and whose maturity rating was no more than three at his fourteenth birthday, needed reassurance and patient explanation. However, the fact that they ask only about their height should not lead one to believe that growth is their primary concern —they want to be tall, but it is their slowness to mature which deeply disturbs them.

MEDICAL FINDINGS

The proper medical examination of members of this age group requires that one know something of an adolescent's attitude toward health and that some of the findings be interpreted in terms of the patient's age. Adolescents tend to deny that there is anything wrong with their health; they resent the implication that there is anything abnormal about them. The adolescent wants to be like everybody else: in his presence it is well to avoid careless comments about something "interesting" or about some "abnormality" which has been found. Most important to remember with this age group is that it is now time that the physician become the boy's doctor, that he go to his physician alone and with his problems. No longer is he a little boy being brought by his mother with her problems.

There are not only special things to look for but there are also certain findings apparently to overlook when one examines these young people.[7] Systolic hypertension is common, particularly in those who are not used to going to a doctor but it is only very rarely that it has an organic basis. It may, however, be of real significance: a fair proportion of those adolescents who have considerable systolic hypertension at a medical examination may be the tense, anxious, or even hypertensive adults of tomorrow, and they would do well to learn to live in a more relaxed fashion. Albuminuria is fairly common, but it is usually of the orthostatic type. Its most important aspect is the frequent need to reassure both parent and boy that its presence does not indicate the existence of serious renal disease.

A frequently misinterpreted finding in adolescence is the basal metabolic rate. If the mother is being given thyroid extract or if the boy is overweight or is doing poorly in school, a mother may suggest that the boy have a metabolism test. The chances of the metabolic rate being somewhere between minus ten and minus thirty are far from remote, but it is most unlikely that to give him thyroid extract will be necessary. Even if his thyroid is, at that particular time, apparently less active than normal, there is no reason to believe that it will not soon adequately adjust itself. If rare instances when a boy's skin is very dry, his behavior sluggish, his heart rate and metabolic rate persistently low, and his serum cholesterol high over a considerable period of time, the use of thyroid extract in doses adequate to constitute a therapeutic test is justifiable. In the usual case, however, it is much sounder medicine and infinitely better

mental hygiene patiently to explain how frequently normal variations in growth pattern and thyroid behavior occur.[1, 16]

What thyroid extract can accomplish for those rare patients who need it is well known. Fig. 4 shows what *time* can do. At age 13 years 8 months this young boy weighed 127 pounds and was 61.6 inches tall. Two years later, at the time the lower photographs were taken, his weight was 132 pounds and his height 67 inches.

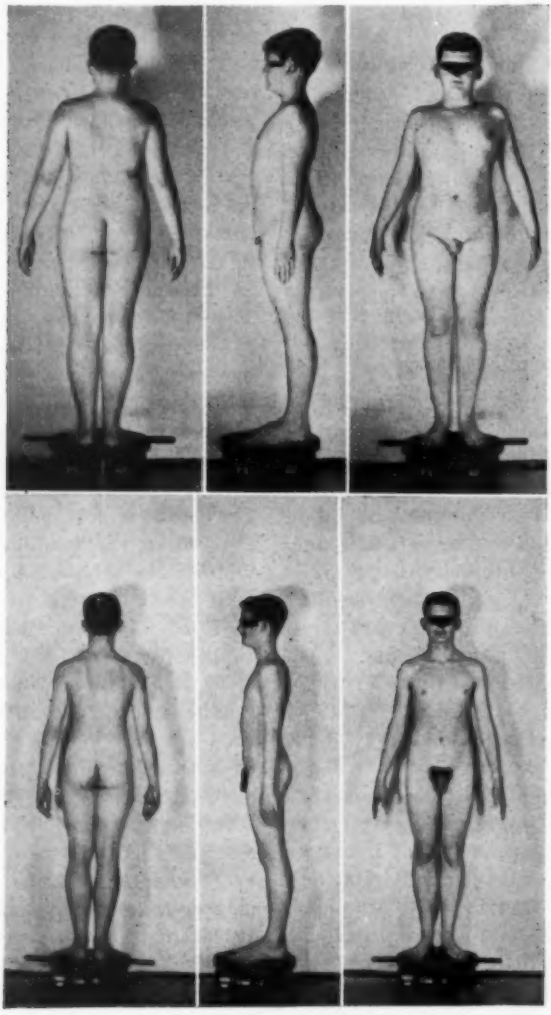


Fig. 4.—The upper photographs show a boy of 13 years 8 months and the lower ones show the same boy two years later. No therapy was used.

At an adolescent's medical examination there are a few matters to consider which are of more importance to him than to younger or older people. Acne is the bane of his existence.[2] It is just as important to try to treat it as it is to explain its relationship to the maturation process. Status of color vision is of importance to the boy who plans a career in the Army, Navy, Air Corps, or Merchant Marine. A pilonidal sinus excludes many a boy from the NROTC program. Plantar warts interfere with his athletics. A testis still undescended after puberty has begun will probably require an operation. Not of least importance at the adolescent's medical examination is his chance to ask questions, to talk over things which may have bothered him. It is better to give him a chance to talk, an opportunity to ask questions, than it is to make suggestions: the relationship the physician builds up with him may do more for him than much of the advice the physician can give.

Low back pain is a symptom which is all too common in adults and which unfortunately is not unusual in adolescents. In this age group whenever there is persistent low back pain, it is imperative that x-rays be taken to determine whether or not such a disorder as epiphysitis or spondylolithesis is present. Strapping with adhesive, heat, sleeping on a bed board all help, at least during the acute stage, but in order to prevent recurrences it is well to consider the advisability of so strengthening the erector spinae muscles that they may subsequently be capable of carrying a greater proportion of the task of supporting the back.

Progressive resistance exercise has been found effective in strengthening the hyperextensors of the trunk. A small group of patients[3] who have been given this type of exercise (but only after careful clinical and x-ray examination) have apparently been considerably benefited.

EMOTIONAL AND PERSONALITY DISORDERS

Severe psychiatric disorders are not common in adolescence, but the number of these young people who have minor disturbances of their mental health is large.[14] The more serious demands and problems which face them in later life—marriage, getting a job—are not yet theirs, but failure in school, parents' divorce, death of a friend, failure to mature or grow, rebellion, excessive dependence, antagonistic feelings toward either parent, lack of friends—any of these can act as a precipitating factor in the development of a disorder which should have attention. Each will react to such factors in a different way. To change from school to school will mean nothing to one boy and may thoroughly upset another who is more dependent or who needs the support of friends about him. A harsh, critical father may bother one boy very little, another will be in a turmoil of rebellion against all for which that father stands.

Adolescents' mental disorders have two characteristics in which they differ from an adult's: their disorders often appear to be of much worse prognosis than subsequently turns out to be the case, and they usually talk more freely and respond more rapidly to treatment than do adults. The term schizoid is often used too loosely in describing an adolescent's be-

havior. An adolescent may be very confused and disturbed and yet make a rapid recovery; his symptoms may be similar to those of an adult who really is schizoid, but the course of his illness is so frequently different from the adult's that the term's implications make its casual use ill-advised. This is not to say that all these young people need is a friend or a patient listener: frequently they need much more than that. However, they do seem to benefit most when they are not regarded in too pessimistic a fashion and when their symptoms are thought of in terms of their years and not as an adult's would be.

SCHOOL FAILURE

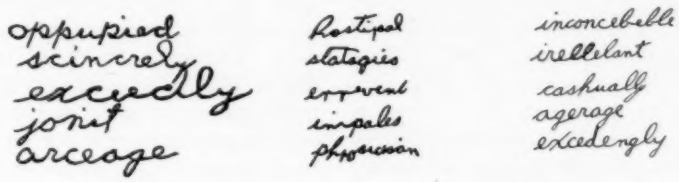
Failure in school is of so much importance to an adolescent that it often has to be considered in relation to some of his physical and psychological difficulties. Nausea, headache, fatigue, behavior problems—all those and many more can and do arise out of failure in school. Rapid growth, low metabolic rate, anemia, eyestrain, and fatigue are too frequently blamed by the parent for the child's failure, and an emotional disorder too often overlooked.

The causes of failure in school are many.[14] It is just as desirable that headache be recognized as a possible symptom of failure in school as it is that anemia not be uncritically accepted as the cause of low marks. An objective approach with an orderly, thorough investigation of the possible physical causes, then an evaluation of such factors as intelligence, proper grade placement, conflicting interests, the presence of a specific language disability, and finally an investigation of personality and emotional factors is essential. Lack of friends, rebellion against a parent, disinterest in the type of studies, confusion because of a friend's death or his parents' divorce may so affect a boy as to make him appear stupid, lazy, or indifferent to the teacher. Not to be forgotten is the "slow starter," the boy who for some unknown reason plods along in a mediocre way for years, gradually improves, and finally confounds the wisdom of teachers and the validity of tests by becoming an outstanding scientist or lawyer.

One cause of scholastic failure, the specific language disability, is worth special consideration.[4, 9, 14] Between 5 and 10 per cent of boys find it difficult to read, they spell in a bizarre fashion, have cramped, uneven handwriting, may have some speech disorder, and may give a history of similar handicaps in other members of their family. A considerable number of these boys are ambidextrous or have evidence of a mixture of cerebral dominance such as right handedness and left eyedness. As they grow older and their difficulties in school increase they may show the effects of discouragement and frustration. Early recognition of this condition can prevent a good deal of trouble. It is best that these children defer for a year or two—until they are ready—the time they start to read and spell, that every effort be made to develop their visual, auditory, and kinesthetic imagery for symbols, that they be given drill in phonetics, that they *not* be taught to read by the "flash card" method.

Some, whose disability is not severe, and whose intelligence is high, are able to get through the early grades but begin to fail when faced with the more

difficult work of high school. In Fig. 5 are reproduced the handwriting and spelling of three 15-year-old boys of high intelligence. The uncertainty of their handwriting is shown in the variation in slant, the differences in pressure, the retracing. Reversals of letters, omission of syllables, and the confusion of one sound and letter for another are obvious. These three boys were also poor silent and oral readers and in the family of each another member handled words poorly.



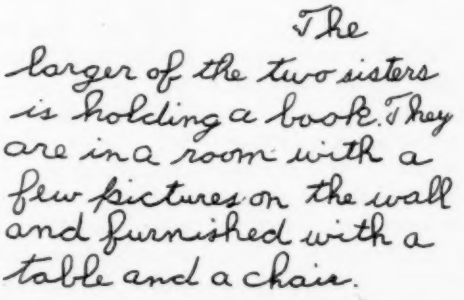

The
larger of the two sisters
is holding a book. They
are in a room with a
few pictures on the wall
and furnished with a
table and a chair.

Fig. 5.—Reproduction of parts of a written spelling test given three boys who had a specific language disability. The excerpt from a theme was written at the same time by the boy whose spelling is shown at the upper left.

The brief excerpt from a theme at the bottom of Fig. 5 is included to illustrate the point that these cases may go undetected if one inspects only writing in which the boy had a free choice of words. That excerpt is from a theme written on the same day by the same boy whose spelling is shown at the upper left in Fig. 5. He had learned to write without error within his own small vocabulary.

Patient, meticulous drill on phonetics, the building of strong association patterns between the sound, the appearance, and the feeling (in writing) of letters produced within a year vast improvement in those boys' fundamental skills. The teaching techniques used are undoubtedly of primary importance, but the psychological effect of having someone recognize and help such boys with the source of their frustration and failure must be of considerable importance.

An inspection of a spelling test is the best single means of detecting this type of trouble: it is the kind, not the number, of errors which suggest the diagnosis. It is important to distinguish these children from that

much larger group who through lack of interest, low intelligence, poor teaching, or some emotional or personality disorder, read poorly. Many of those children may respond very well to various methods designed solely to increase their reading efficiency either by direct attack upon it or by attempts to motivate them or by efforts to resolve their emotional conflicts.

Eyeglasses, vitamins, more rest, iron, tonics, thyroid extract, or more discipline will not solve the problems of the boy who fails in school because of lack of interest, low intelligence, a language disability, or the confusion and anxiety growing out of a personality or emotional disorder. Anemia, rapid growth, metabolic disorders, and poor vision or hearing all are important, but only rarely is a single handicap as significant as is the nature of the boy's personality, aptitudes, and adjustment.

ATHLETICS

Adolescents take games seriously. They are important to them as an outlet for their excessive energy, as exercise, as an opportunity to learn cooperation, and as a means of learning to win and lose gracefully. Not to appreciate their significance to a boy, casually to suggest that a boy give up a game is to make a considerable error.

There are very few adolescents who should not be allowed to compete in athletics. The danger of their being strained if they are properly conditioned,[10] or of their being injured if they are adequately protected,[17] should not be a deterrent. A boy who has heart disease can play in the goal at soccer, hockey, or lacrosse: it is more desirable to try to make him feel he can be part of a group than it is to overprotect him. More exercise rather than more rest is the proper prescription for the boy who tires too easily because he is in poor condition: the more he takes it easy, the more fatiguing will subsequent exercise become—too much restriction, too much solicitude, too much rest not only make a boy vulnerable to fatigue but also start him on the way to becoming self-centered and neurotic.

Knee injuries are so common and often so serious in adolescents that they deserve some special consideration. The management of the knee sprain during its acute stage needs little comment, but in its care during convalescence a few points which have general application are sometimes forgotten.[8] An adolescent's knee will not be strong enough so that he should return to athletics until it has become as strong as his uninjured leg. For the knee to have regained full extension and flexion, to be free of pain and fluid, and to strongly resist the examiner's hand is not enough. Ideally the quadriceps strength should be increased so that it has become stronger than it was when the injury occurred. Progressive resistance exercise[8] is a technique which during the past few years has proved to be a very useful adjunct in the physical therapy of knee injuries. An adolescent's response to this type of treatment is much more enthusiastic than is his reaction to the suggestion that he wait for nature to heal him.

These are a few of the matters which are of importance to adolescents. There are few baffling problems if one learns a little about their

attitudes, behavior, needs, and physiology. They want—and need to be—regarded as people, not as problems. Their outstanding characteristic is their capacity for change: neither their attitudes nor behavior nor physiology has yet settled into their adult mold. That is the only reason for it being at times difficult to understand them and their ailments—it will continue to be particularly so if one attempts to judge them by adult standards.

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AUREOMYCIN TREATMENT OF DIPHTHERIA AND DIPHTHERIA CARRIERS

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PENICILLIN has been successfully employed in the treatment of both acute diphtheria and the diphtheria carrier.[1] In acute diphtheria, not only has the patient been cleared of *Corynebacterium diphtheriae* and further toxin production has thereby been arrested, but the secondary invaders which were responsible for some of the complication were also eliminated. As a result of these experiences, we have advocated that all acute diphtheria patients be treated with antitoxin and penicillin. Considerable but not universal success has also been attained in the treatment of diphtheria carriers with penicillin. The carrier state has been eliminated in over 75 per cent of the patients so treated. While most strains of *C. diphtheriae* were susceptible to concentration of penicillin easily obtained, some strains were or had become resistant to concentrations attained by the administration of as much as 1,000,000 to 2,000,000 units of penicillin daily.[2] It is quite possible that with larger doses of penicillin, most of the resistant strains of *C. diphtheriae* could be eliminated; nevertheless Buxbaum and associates[3] have shown that some strains resist concentrations of penicillin as high as 50 to 100 units per milliliter, levels not readily obtained. Thus the problem of eliminating *C. diphtheriae* from those patients carrying penicillin-resistant strains still exists.

From the Willard Parker Hospital.

The determination of the antidiphtheritic action of other antibiotics was a logical sequence to our experiences with penicillin. In vitro studies[4] have demonstrated that *C. diphtheriae* is susceptible to aureomycin, in readily attainable levels. We proceeded therefore to determine the clinical effect of aureomycin in cases of acute faucial diphtheria and in diphtheria carriers.

Thirteen patients with faucial diphtheria and eleven diphtheria carriers were treated with 25 to 50 units of aureomycin per kilo per day. Every patient with acute diphtheria was also given diphtheria antitoxin in the usual dosage as soon as the disease was suspected.

The results are recorded in Table II and Charts 1 and 2. Of the thirteen patients with faucial diphtheria who were treated with both antitoxin and aureomycin, three had negative nose and throat cultures for *C. diphtheriae* within twenty-four hours, two in two days, two in three days, two in four days, one in six days, one in ten days, one in twelve days, and one in nineteen days. This represents an average of five days as compared to an average of twenty-one days in patients treated with antitoxin alone in previously collected cases at the Willard Parker Hospital. Aureomycin was of no value in preventing toxic manifestations in one patient admitted with a bullneck. This man 37 years of age died of myocarditis even

though the *C. diphtheriae* had been eliminated while he was on aureomycin.

The results of aureomycin in the diphtheria carriers were less gratifying. Of the eleven patients treated, tients were discharged from the hospital for further medical care or at the request of the patients' families after only one negative culture. Description of the course of these six patients is summarized in the text.

TABLE I. RANGE OF CONCENTRATIONS OF NINE ANTIBIOTICS WHICH COMPLETELY INHIBIT MORE THAN 80 PER CENT OF VIRULENT STRAINS OF C. DIPHTHERIAE*

ANTIBIOTIC	MINIMUM COMPLETE INHIBITING CONCENTRATIONS, MICROGRAMS PER MILLILITER	PER CENT OF STRAINS
Bacitracin	0.2-0.4	89
Penicillin	0.2-0.8	86
Terramycin	0.8-3.1	92
Chloromycetin	1.6-6.3	92
Neomycin	1.6-6.3	83
Aureomycin	3.1-6.3	83
Streptomycin	3.1-6.3	83
Aerosporin	100-200	92
Polymyxin	>200	100

*Reproduced through the courtesy of Dr. M. Finland and The Journal of Pediatrics 37: 718, 1950.

TABLE II. PATIENTS WITH DIPHTHERIA AND DIPHTHERIA CARRIERS WHOSE CULTURES BECAME NEGATIVE DURING AUREOMYCIN THERAPY AND REMAINED NEGATIVE AFTER AUREOMYCIN WAS DISCONTINUED

NAME	AGE	TYPE OF DIPHTHERIA (CARRIER OR ACTIVE)	DOSAGE OF AUREOMYCIN MG./KILO/DAY	DURATION OF POSITIVE CULTURES (DAYS)
W. B.	32 yr.	active	25	2
C. R.	11 yr.	active	25	4
S. B.	13 yr.	active	25	1
A. M.	6 yr.	active	25	2
M. G.	17 yr.	carrier	25	1
C. W.	12 yr.	carrier	25	2
E. B.	5 yr.	carrier	25	1
L. C.	25 yr.	carrier	50	3
R. T.	3 yr.	carrier	50	10
D. D.	7 mo.	active	50	10
M. W.	2 yr.	active	50	1
R. B.	9 yr.	active	50	3
J. R.	1 yr.	active	50	4
M. R.	8 mo.	active	50	19
E. D.	8 yr.	active	50	3
E. S.	11 yr.	active	50	6
B. S.	12 yr.	active	50	1

two developed negative throat cultures in one day, one in two days, one in three days, and one in ten days. Of the other six patients, four were infected with nonvirulent strains of *C. diphtheriae*. For this reason and because being diphtheria carriers was incidental to other diseases these pa-

CASE 1.—P. S. (No. 4696), a 57-year-old man ill with chronic nephritis, was a carrier of a nontoxic strain of *C. diphtheriae*. He was given 50 mg. per kilo of aureomycin per day. The throat culture became negative on the sixth day of treatment. Because of vomiting resulting in dehydration, the drug was discontinued after only

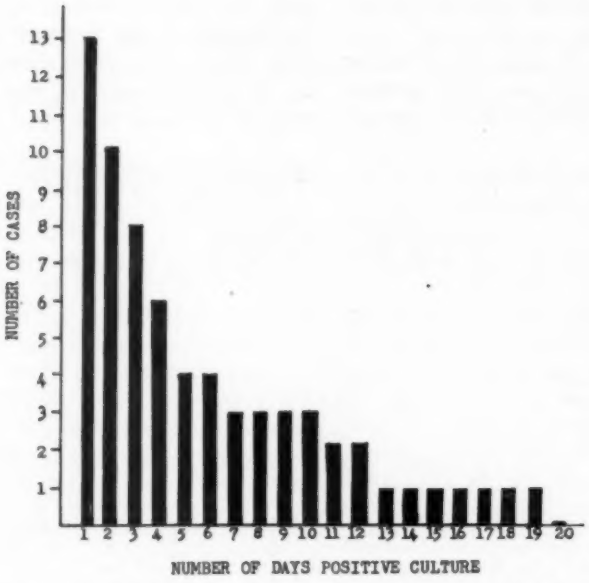

Chart 1.—Effect of aureomycin on throat cultures of patients with diphtheria.

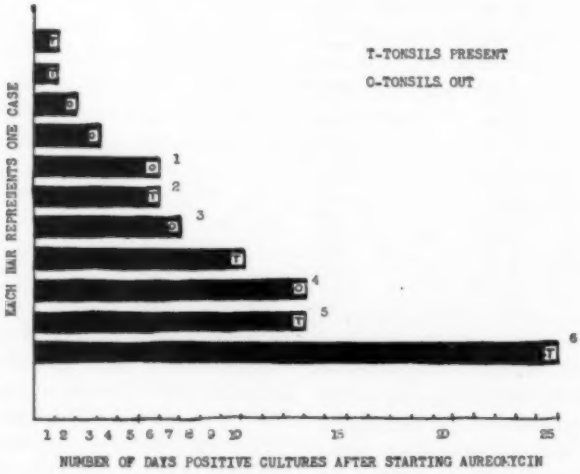

Chart 2.—Effect of aureomycin on diphtheria carriers.

one negative culture. Further cultures were not taken at the Willard Parker Hospital since the patient was transferred to another hospital. It was later learned that the throat culture remained negative.

CASE 2.—C. I. (No. 5510) was a 5-year-old female whose culture became negative after two days of aureomycin, 50 mg. per kilo. The drug was continued after the three negative cultures were obtained because of a pharyngitis and high fever which developed while on the antibiotic. Cultures remained negative for five days but became positive again on the sixth, while still receiving aureomycin. She was discharged because the *C. diphtheriae* was nontoxic.

CASE 3.—P. B. (No. 1818) was a 9-year-old male carrier who received aureomycin for seven days (25 mg. per kilo) without attaining negative cultures. Since the organism was nontoxic his parents took him from the Willard Parker Hospital and returned him to another institution for further ACTH treatment of his rheumatoid arthritis. He had no tonsils.

CASE 4.—T. Mc. (No. 4244), a 13-year-old male, received aureomycin 50 mg. per kilo for ten days, 100 mg. per kilo for three days, then aureomycin troches for one day. One negative culture was obtained after the one day of troches. He requested and was granted permission to leave the hospital because the organism was nontoxic.

CASE 5.—F. C. (No. 3188), a 15-year-old male, was treated for thirteen days with aureomycin 50 mg. per kilo without result for a chronic draining ear which contained *C. diphtheriae* and the Friedländer bacilli. These organisms were also present in the nose and throat. The *C. diphtheriae* was nontoxic. Five days after oral aureomycin was stopped, aureomycin ear drops were started. The ear cultures became negative for *C. diphtheriae* after one day. However, the nose and throat cultures continued to be positive even when aureomycin drops were added to the local ear therapy. Cultures for both *C. diphtheriae* and Friedländer bacilli became negative after the patient had received a total of 6 Gm. of dihydrostreptomycin over a four-day period or 1.5 Gm. per day.

CASE 6.—(No. 4777.) The nose and throat cultures of this 8-year-old girl became negative in six days on aureomycin 50 mg. per kilo. Four days after aureomycin was discontinued the cultures became positive and remained so. Aureomycin was restarted but the cultures were not reversed after another five days of treatment. Penicillin (aqueous) was therefore started, giving 250,000 units every six hours intramuscularly. The cultures became negative in one day and remained so for the next four days of penicillin therapy. Three days after penicillin was discontinued the cultures were again positive. Intramuscular procaine penicillin, 300,000 units twice daily, plus penicillin troches, one every two hours, were started and continued for ten days without eliminating *C. diphtheriae*. The organism was found to be sensitive in vitro to aureomycin, streptomycin, and Gantrisin, but resistant to penicillin.

It is noteworthy that one patient (Case 2) reverted to a positive throat culture after being negative for five days. This patient would have been considered cured and discharged after three negative cultures in accordance with health department standards.

The history of Case 5 is of particular interest because it demonstrates a successful elimination of *C. diphtheriae* with streptomycin after both penicillin and aureomycin alone or in combination had failed to eradicate it from the pharynx and from a draining ear. Incidentally this boy was also infected with the Friedländer bacillus which like the *C. diphtheriae*

failed to respond to penicillin alone, aureomycin alone, and to both given simultaneously, and responded only to the streptomycin.

In summary, aureomycin, in dosage of 25 to 50 mg. per kilo of body weight given in four equal doses each twenty-four hours, shortened the carrier period for *C. diphtheriae* in thirteen patients with faucial diphtheria and in five possibly six out of thirteen diphtheria carriers. It did not prevent the development of toxic myocarditis in one very sick patient. He died from the toxic myocarditis.

Although the number of cases is small, the results seem significant and indicate the possibility of using aureomycin *along with diphtheria antitoxin* in cases of acute diphtheria and alone in cases of diphtheria carriers. Aureomycin would be especially indicated in those individuals who harbor strains of *C. diphtheriae* which shows resistance to penicillin and in individuals who are allergic to penicillin. In some cases both antibiotics might be used together. Possibly greater success might be attained by larger doses of aureomycin although failure on 100 mg. per kilo per day was experienced twice.

It is noteworthy that streptomycin was effective against one strain of *C. diphtheriae* which failed to respond to both penicillin and aureomycin. Streptomycin might be tried in other cases of diphtheria and in diphtheria carriers. The in vitro data also suggest that terramycin and other antibiotics may be effective. Studies of the effect of terramycin are in progress.

CONCLUSIONS

Aureomycin is an effective agent against *C. diphtheriae*. Dosage of 25 to 50 mg. per kilo of body weight given daily helps to shorten the carrier period of some patients with acute faucial diphtheria and of diphtheria carriers. Aureomycin is indicated in the treatment of diphtheria only if added to antitoxin. It is not antitoxic.

It may be particularly useful in diphtheria patients harboring penicillin-resistant strains of *C. diphtheriae* and in individuals intolerant of penicillin.

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THE TREATMENT OF PERTUSSIS WITH AUREOMYCIN, CHLORAMPHENICOL, AND TERRAMYCIN

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A NUMBER of antibacterial agents have been found to be effective against *Hemophilus pertussis* in the test tube; the most active is polymyxin.[1-8] There has been almost universal agreement in the literature that aureomycin,[9-14] chloramphenicol,[15-24] and terramycin[25-27] modify the clinical course of whooping cough. One of the most recent reports on this subject expresses the opinion, however, that "the specific drug for complete and successful treatment of pertussis still lies in the future."[28]

The purpose of this paper is to record the failure to influence beneficially the clinical course of pertussis with either aureomycin, chloramphenicol, or terramycin, and to point out that secondary bacterial and mycotic infections occur during treatment with any of these agents. When compared with patients receiving no antibacterial therapy, it will be shown that the incidence of such complications in treated patients is not significantly reduced by chemotherapy although the microorganisms involved in them are different. Important changes in the bacterial flora of the upper respiratory tract will be described and their relation to the antibiotic agents studied discussed.

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METHODS

Patients with pertussis without complications at the time of admission to the hospital were the only ones included in the study. All children with fever which was not clearly due to dehydration were eliminated. A diagnosis of pertussis was made when two or more of the following findings were positive: the clinical history and course of the illness, contact with a proved case of whooping cough, isolation of *H. pertussis* from the upper respiratory tract, and leucocytosis with significant relative lymphocytosis.

Eighty patients were treated; nineteen received aureomycin, twenty-five terramycin, and thirty-six chloramphenicol. The drugs were administered orally whenever possible, in divided doses (every six hours), and in quantities ranging from 50 to 75 mg. per kilogram of body weight per day. If vomiting or extreme youth of a patient precluded administration by mouth, the antibiotic agents were given rectally—100 mg. per kilogram per day. Treatment was continued in most instances for fourteen days. Almost all of the children less than 1 year of age received, in addition, three injections of 20 c.c. of human hyperimmune serum at forty-eight-hour intervals. Careful attention was

paid to maintenance of adequate hydration and electrolyte balance. If vomiting occurred after feeding, food was offered again immediately until it was retained.

Temperature, pulse, and respiratory rates were recorded every four hours. If the rectal temperature rose to 101° F. or higher the following studies were carried out: (1) complete physical examination, (2) culture of the blood, nose, and thoat, (3) urinalysis, (4) white blood count and differential, and (5) roentgenographic study of the lungs. Determinations of plasma chloride and carbon dioxide were made in every instance where acidosis was suspected. Physical examinations were carried out daily.

All of the cases were isolated in a single ward in which a nurse was in constant attendance. Whenever possible, the same three nurses divided the day into three eight-hour shifts and had no other duties. They were instructed in the counting of paroxysms which were recorded, immediately after their occurrence, on a special form posted at each bedside. All patients were observed at frequent intervals during the day by various members of the house staff and by one or more of us.

Cultures of the upper respiratory tract were made by means of the "nasopharyngeal swab" at the time of admission to the hospital and at least three times weekly thereafter until discharge. They were planted on both Bordet-Gengou and on heart infusion-yeast-tryptose peptone-blood agar. All of the colonies appearing on these two media were isolated and identified, wherever possible. White blood counts with differentials were made a minimum of twice a week.

RESULTS

Effect of Chemotherapy on Paroxysms of Coughing.—Nineteen patients were treated with aureomycin. Thirteen were less than 1 year and the remainder were between 1 and 6 years of age. Thirteen had had paroxysms for one week or longer before chemotherapy was instituted; of these, five had been coughing for two weeks or more. Nine patients received antipertussis serum in addition to the antibiotic. In Table I are presented the number of paroxysms occurring during the entire period of observation. The smallest and largest number of attacks of whooping or coughing per day in the week are given. The data were analyzed in this manner because it was thought that a trend toward improvement would be more apparent than if a simple day-to-day analysis were made since it had become evident early in the study that rapid and marked interruption of the clinical course of the disease was not produced by any of the drugs and that, in many instances, coughing persisted for as long a time as in untreated patients. While in a few patients, for example Nos. 1, 5, 10, and 11, there appeared to be amelioration of the disease after one week of therapy, this cannot be accepted as proof of the effectiveness of the antibiotic. Many children who receive no specific therapy and who have relatively mild infections do not have "whooping" of a remarkable degree beyond two weeks. It is important to stress that, in the evaluation of chemotherapy in pertussis, the point in the disease at which treatment is started must be taken into consideration. Decrease in the number of paroxysms after one to

TABLE I. INFLUENCE OF AUREOMYCIN ON PAROXYSMS OF PERTUSSIS

CASE NO.	DAYS OF PAROXYSMS PRIOR TO TREATMENT	DAYS OF THERAPY	HYPER-IMMUNE SERUM	WEEK OF HOSPITALIZATION—SMALLEST AND LARGEST NUMBER OF PAROXYSMS PER DAY IN WEEK			
				1 WK.	2 WK.	3 WK.	4 WK.
1	2	13	0	0- 1	0- 3	2- 4	--
2	2	14	+	0- 5	0- 6	1- 5	
3	3	15	0	0- 7	0- 2	0- 3	0- 1
4	3	9	+	2- 7	0- 3	--	--
5	4	11	0	3-14	1- 6	--	--
6	5	6	+	3-18	3-11	4- 9	--
7	7	15	+	10-19	8-16	8-11	3-14
8	7	17	0	7-21	2-14	0- 1	--
9	7	15	0	5-18	6-14	8- 9	--
10	7	14	0	3-10	1- 5	--	
11	7	14	+	0- 5	0- 1	0- 1	--
12	7	14	0	0- 3	0- 4	0	--
13	9	10	+	6-15	5-10	2-11	1- 6
14	10	10	+	5-11	3- 8	0- 3	
15	14	14	+	5-15	2-11	2- 4	0- 2
16	14	14	0	5-20	6-11	2- 7	--
17	14	14	0	4-11	2- 7	0- 7	
18	21	14	0	2- 5	1-12	0- 6	0- 5
19	21	8	+	0- 1	0- 3	0- 2	--

TABLE II. INFLUENCE OF CHLORAMPHENICOL ON PAROXYSMS OF PERTUSSIS

CASE NO.	DAYS OF PAROXYSMS PRIOR TO TREATMENT	DAYS OF THERAPY	HYPER-IMMUNE SERUM	WEEK OF HOSPITALIZATION—SMALLEST AND LARGEST NUMBER OF PAROXYSMS PER DAY IN WEEK			
				1 WK.	2 WK.	3 WK.	4 WK.
1	7	14	0	2-12	1- 8	0- 4	
2	14	14	0	3-14	0- 5	0- 1	0-1
3	21	15	+	3-13	2-18	0- 1	
4	7	14	+	3-20	1- 7	0- 5	0-2
5	5	14	+	6-23	0- 9	0- 2	
6	6	12	+	0- 2	0- 2	0- 2	
7	7	12	0	2- 8	5-20	7-16	1-8
8	14	14	+	1- 9	0- 4	0- 5	
9	8	13	+	1- 6	0- 2	1- 4	0-2
10	10	16	+	2- 8	0- 4	0- 5	
11	7	14	0	1- 9	3-16	1- 5	
12	10	10	+	2- 7	1- 8	0- 1	
13	3	14	+	2- 8	0- 3	0- 3	0-3
14	2	14	0	0- 1	0	0	0
15	5	14	0	0- 4	0- 2	0- 1	
16	3	14	+	0- 2	0	0	
17	3	14	+	4-10	5-10	0- 8	
18	6	12	0	1-13	0- 2	0- 1	
19	14	14	0	1- 4	0- 6	2- 6	
20	7	14	0	4-19	3- 8	1-11	
21	10	14	0	0- 1	0- 2	0- 1	
22	1	14	+	0- 2	0- 1	0- 1	
23	7	16	0	2- 7	5-10	0- 7	0-2
24	6	20	0	4- 8	1- 7	0- 4	0-8
25	7	14	0	2-21	0- 4	0- 2	
26	3	14	+	2- 5	0- 4	0	
27	8	20	0	1- 6	0- 4	0- 1	
28	7	12	0	1- 6	0- 2	0- 1	
29	1	14	0	10-15	1-14	6-13	3-6
30	5	14	0	6-10	5-13	1- 6	
31	1	14	+	2- 7	1- 4	1- 7	
32	2	15	+	7-14	3-11	0- 6	
33	4	15	+	2-28	0- 3	4- 9	1-6
34	7	11	+	0- 1	0	0	0
35	60	9	0	0- 1	0- 1	0- 1	0
36	2	6	+	0- 1	0	0- 2	0-1

two weeks of administration of a drug in children who have been "whooping" for two to three weeks prior to treatment cannot be accepted as indicating a therapeutic effect, since this is the natural history of the disease in many instances without the use of any "specific" measures. The data in Table I indicate that aureomycin had little or no effect in reducing the incidence of paroxysms of coughing. No differences could be detected between those given both antiserum and chemotherapy and those receiving antibiotic alone.

Thirty-six patients were treated with chloramphenicol. Nineteen were less than 12 months of age; of these, sixteen received hyperimmune antipertussis serum in addition to chemotherapy. The data relative to paroxysms of coughing are presented in Table II. While in a few cases (1, 2, 4, 5, 25, and 33) there appeared to be an appreciable reduction in the number of attacks, there were as many instances in which no effect was noted; in some patients (7, 11, 17, 29, 31) the maximum number of paroxysms in one of the weeks during or after treatment was as great or greater than that experienced in the earliest phases of therapy. As with aureomycin, the reduction in coughing in a number of the children may be accounted for by natural healing of the disease, if the duration of paroxysms prior to the institution of chloramphenicol is taken into consideration. The data suggest that this drug exerts no remarkable effect on the paroxysmal phase of whooping cough.

Twenty-five children with uncomplicated pertussis received terramycin.

TABLE III. INFLUENCE OF TERRAMYCIN ON PAROXYSMS OF PERTUSSIS

CASE NO.	DAYS OF PAROXYSMS PRIOR TO TREATMENT	DAYS OF THERAPY	HYPER-IMMUNE SERUM	WEEK OF HOSPITALIZATION—SMALLEST AND LARGEST NUMBER OF PAROXYSMS PER DAY IN WEEK			
				1 WK.	2 WK.	3 WK.	4 WK.
1	3	14	+	3-10	0- 7	0	0
2	21	14	0	0-12	0- 4	0- 1	
3	5	14	+	5-12	3-10	2- 5	
4	9	14	0	9-15	3-13	3- 5	0-2
5	4	14	+	3- 8	4- 8	1- 7	1-3
6	3	16	+	4-11	3- 9	0- 3	0-4
7	6	15	+	2- 7	0- 3	0- 1	0
8	7	14	0	0- 8	3- 7	0- 3	0
9	7	12	0	2- 8	0- 4	0	
10	3	12	+	3- 7	0- 3	0	
11	2	12	+	0- 5	0- 2	0- 1	0
12	6	14	+	0- 5	1- 7	0	
13	7	12	+	0- 6	0	0	
14	9	12	0	3-18	1- 2	0- 2	0
15	1	14	+	1-10	0- 1	0	
16	14	12	+	0- 7	0- 1	0	
17	5	14	+	3- 6	3-10	1-14	
18	2	16	0	4-27	6-18	4-11	0-3
19	–6	16	0	0- 8	2-17	2- 7	0-3
20	4	12	+	10-23	3- 9	1- 5	1-3
21	7	12	+	4-10	2- 6	0	
22	14	16	0	5-13	0- 5	1- 4	
23	1	14	0	0- 8	2- 6	0- 2	
24	1	15	+	1-10	1- 6	3- 5	
25	14	16	0	2- 8	4-15	0- 4	

Fourteen were less than 1 year of age; thirteen of these were younger than 6 months. Hyperimmune serum was given to all but three of the patients younger than 1 year. The results produced by terramycin (Table III) were approximately the same as those observed when aureomycin or chloramphenicol were used. With the exception of a few cases (7, 10, 14, 15, 20) in which there was a suggestion of a slight decrease in the number of paroxysms as a result of chemotherapy, most of the others showed no appreciable reduction in coughing. Case 19 is of particular importance in pointing out the failure of terramycin to influence the clinical course of pertussis. This child was exposed to a known case and admitted to the hospital in the catarrhal phase of the disease six days prior to the onset of paroxysmal coughing; the diagnosis was established by isolation of the organism. As can be seen in Table III, the number of paroxysms was greater in the second week of treatment than in the first and coughing continued for four weeks. If terramycin were truly effective in whooping cough, this is the type of case in which the best response could have been expected.

Bacteriologic Studies.—H. pertussis was isolated from thirteen of the patients, subsequently treated with aureomycin, at the time of admission to the hospital. In four (30.8 per cent) the organisms could not be recovered after forty-eight hours of therapy. In the others, they were still detectable from three to nineteen days after institution of treatment. In those receiving chloramphenicol, *H. pertussis* was present in the upper respiratory tracts of fourteen when first examined. Fifty per cent of them were free of organisms within forty-eight hours after administration of the drug was started; the rest retained the bacteria for from four to eighteen days after initiation of therapy. Twelve of the patients treated with terramycin revealed the pertussis bacillus prior to receiving the antibiotic. Of these, ten (83.3 per cent) had negative cultures after forty-eight hours or less of treatment. The other two patients had positive cultures for only ninety-six hours. The data presented in Table IV show that neither

TABLE IV. DURATION OF POSITIVE CULTURES FOR H. PERTUSSIS

PATIENTS WITH + CULTURES ON ADMISSION	TYPE OF TREATMENT AND DAYS AFTER INITIATION OF THERAPY ON WHICH CULTURES WERE STILL POSITIVE		
	AUREOMYCIN	CHLORAMPHENICOL	TERRAMYCIN
1	1, 2	1, 4, 16, 18	1
2	1	1, 4	1, 4
3	1, 4	1	1
4	1, 12, 19	1, 7	1
5	1, 19	1	1, 2
6	1	1, 4, 5	1, 2, 4
7	1, 3	1, 2	1, 2
8	1, 2, 5	1	1
9	1, 7	1, 2	1
10	1	1, 2, 4, 5, 6	1
11	1, 6	1, 6, 7, 9	1
12	1, 2, 10	1	1
13	1, 4	1, 2, 6	--
14	--	1	--

aureomycin nor chloramphenicol produced prompt eradication of *H. pertussis* from the respiratory tract in all cases and that, in some instances, the organism was still present even after the conclusion of treatment. Terramycin appeared to be the most active in eliminating the infecting agent from the nasopharynx.

Careful bacteriologic studies were carried out in every case in order to determine the changes in the bacterial flora of the nasopharynx which occurred during the period of therapy. Not all of the organisms isolated, e.g., *Streptococcus viridans, Neisseria catarrhalis, Staphylococcus albus,* are included in Table V. This shows the incidence of recovery of certain potentially pathogenic organisms which were not detected in cultures taken prior to the institution of therapy but were noted first during the period of treatment. Yeasts and Monilia, *Proteus vulgaris,* and members of the coli-aerogenes group appeared in detectable quantities in an appreciable number of the patients receiving each of the antibiotic agents. Striking was the high incidence of isolations of *Diplococcus pneumoniae* from the children given chloramphenicol. The identity of these organisms was established by their colonial and cellular morphology, bile solubility and fermentation of inulin; most of the strains were types III and VIII. Unfortunately they were not examined for chloramphenicol sensitivity. None of the drugs prevented the appearance of *H. influenzae.* The relation of such changes in the bacterial flora of the respiratory tract to superinfections occurring during treatment is emphasized below.

Complications.—Only those complications which were observed during the period of therapy are discussed here; all were due to secondary bacterial invasion. Of the patients receiving aureomycin, six suffered superinfections while still being treated. Four developed acute suppurative otitis media from which *P. vulgaris* was isolated in pure culture. Two instances of bronchopneumonia were observed. In one, pharyngeal cultures revealed *Escherichia coli, Aerobacter aerogenes,* and *Pseudomonas pyocyanea;* rapid cure followed the administration of streptomycin parenterally. In the other, *Klebsiella pneumoniae* was the predominant organism in the nasopharynx and treatment with sulfadiazine and streptomycin was effective. The total incidence of complications in those treated with aureomycin was 31.2 per cent.

Bronchopneumonia occurred in five cases while receiving chloramphenicol. The causative bacteria in three were the beta-hemolytic Streptococcus, *E.*

TABLE V. BACTERIA ISOLATED FROM UPPER RESPIRATORY TRACT DURING THERAPY

ORGANISM IN CULTURES OF UPPER RESPIRATORY TRACT	TYPE OF CHEMOTHERAPY—PER CENT OF PATIENTS		
	AUREOMYCIN	CHLORAMPHENICOL	TERRAMYCIN
Yeasts and Monilia	37.1	22.16	12
Coli-aerogenes group	100	16.6	20
P. vulgaris	21.2	8.3	20
D. pneumoniae types III and VIII	15.9	41.5	--
β-hemolytic Streptococcus	--	13.7	4
H. influenzae	5.3	11.08	16
Ps. pyocyanea	5.3	--	--
K. pneumoniae	5.3	--	8

coli, and *D. pneumoniae* (type VIII), respectively; in the other two, no definite etiological agent was identified. All of the children recovered after exhibition of aureomycin or penicillin. One patient developed suppurative otitis media due to *P. vulgaris* during treatment and required mastoidectomy after failure of streptomycin and sulfonamide therapy. An acute pharyngitis developed in one youngster on the fifth day of chloramphenicol administration; beta-hemolytic Streptococcus was isolated in large numbers from the throat; penicillin produced prompt cure. The total incidence of complications in this group was 25.77 per cent.

Table VI. Complications Occurring During Treatment

Disease	Aureomycin 19 patients %	Chloramphenicol 36 patients %	Terramycin 25 patients %	No chemotherapy 139 patients %
Bronchopneumonia	10.0	13.85	4	17.1
Suppurative otitis media	21.2	9.15	0	4.26
Strep. pharyngitis	0	2.77	0	0
Monilial stomatitis	0	0	8	0
Total complications	31.2	25.77	12	21.36

Although not completely eliminated, the incidence of complications was lowest with terramycin—12 per cent. Monilial stomatitis was seen only in this group and occurred in 8 per cent. The only serious superinfection was a bronchopneumonia due to *Hemophilus influenzae* which responded promptly to streptomycin.

In order to evaluate critically the effect of chemotherapy on the incidence of secondary bacterial complications in pertussis, the records of 139 patients with this disease who received no drugs were studied. All had uncomplicated whooping cough at the time of admission to the hospital. Their age distribution was the same as the treated patients and about half had received immune serum. The rate of complications in this control group was 21.36 per cent. Bronchopneumonia was the commonest secondary infection and developed in 17.1 per cent. Suppurative otitis media occurred in 4.26 per cent. Thus, the incidence of complications in untreated cases was 10 per cent less than when aureomycin was used and about 4 per cent smaller than when chloramphenicol was given. The only agent which produced fewer complications than were observed in the control group was terramycin.

Analysis of the effect of hyperimmune serum on the occurrence of secondary bacterial infections revealed no significant differences between patients treated with serum alone or with serum and antibiotics and those who received only chemotherapy or were given no specific treatment. These results confirm a previous clinical impression that serotherapy in pertussis is without effect in reducing the incidence of complications. No opinion can be expressed concerning its value in the paroxysmal phase of the disease because this aspect of the problem has not been studied.

DISCUSSION

One of the most vexing problems in attempting to study the effect of vari-

ous types of therapy in pertussis is the selection of valid "criteria for improvement." In the past, emphasis has been placed on the duration and severity of the paroxysmal coughing, the length of hospitalization, the total "duration" of the disease, the rapidity with which fever abates, and the speed of eradication of the causative organisms from the upper respiratory tract. Change in the incidence of "whooping" is probably very unreliable as a criterion for following the clinical course of the disease because it may be influenced by many nonspecific factors. Children younger than 6 months of age frequently do not "whoop." Stimulation by feeding, examination, culturing of the nasopharynx, or drawing blood may precipitate an attack of coughing. Active "whooping" by one patient may induce paroxysms in others in the same room. Defervescence is of no help as an indication of recovery because very little or no fever is present in the uncomplicated paroxysmal stage of pertussis. In the absence of dehydration, fever of any remarkable degree indicates a complication. Length of hospitalization may depend on local quarantine regulations and other social factors and be completely unrelated to the severity of the disease. The "duration" of illness is of little or no value as a criterion of severity or even persistence of the disease unless it is *abruptly* interrupted by chemotherapy. It is not at all rare in untreated patients, for example, for "whooping" to continue for several weeks after the expected termination of the paroxysmal stage. The "whoop" may sometimes reappear, following a mild upper respiratory infection, after it has been absent for some time; this has been referred to as "habit whoop." The rate of disappearance of the causative organisms from the respiratory tract is not a very useful basis on which to evaluate chemotherapy because only about 60 to 70 per cent of cases yield *H. pertussis* at the beginning of the paroxysmal stage and the incidence of positive cultures decreases very rapidly thereafter. It may be impossible to isolate the pertussis bacillus, even when the best available methods are used, in many children in the third and fourth weeks of the paroxysmal phase although "whooping" may still be frequent and severe. One criterion which can be evaluated with ease and accuracy and is of greatest importance to the patient is the development of secondary bacterial infections during the course of the disease. If, as is the case in pertussis, chemotherapy does not produce dramatic interruption of the clinical course such as occurs with penicillin in pneumococcal pneumonia or with streptomycin in tularemia, it is most difficult to ascertain whether or not improvement has taken place because of treatment or as part of the natural history of the disease. For these reasons, the validity of the criteria which have been used for determining the effect of chemotherapy in pertussis is open to question. The incidence of secondary bacterial infections is probably the most useful basis for evaluation of the efficacy of specific treatment in pertussis.

Since many of the patients studied were not treated until one or two weeks of the paroxysmal stage of pertussis had elapsed and since it is not rare for whooping to persist in untreated patients for only two to four weeks, the data obtained in this in-

vestigation indicate that neither aureomycin, chloramphenicol, or terramycin had any noticeable effect in reducing the incidence of coughing. There was certainly no evidence that any of these drugs produced dramatic interruption of the clinical course of the disease. In some children in whom paroxysms had been present for only one to three days when chemotherapy was instituted, cough continued with little change in frequency for two or more weeks. In one youngster treated with terramycin in the catarrhal phase, the development of paroxysmal coughing was not prevented.

Terramycin appeared to be the most efficient of the three agents in eliminating *H. pertussis* from the nasopharynx. Chloramphenicol and aureomycin were of approximately the same degree of activity in this respect. These results, however, are probably of little importance in indicating a beneficial effect of any of these drugs on the clinical course of the disease because, as was pointed out above, there is little relation between persistence of organisms in the upper respiratory tract and continuation of clinical manifestations.

Most disturbing was the demonstration that potentially pathogenic organisms appeared in the respiratory tract during chemotherapy. The frequency with which members of the *E. coli-A. aerogenes* group, *P. vulgaris,* and yeasts and Monilia were found in patients treated with these antibiotics was very striking. A large number of children became carriers of the Pneumococcus while receiving chloramphenicol. That such flora changes were not without clinical importance is borne out by the fact that the secondary bacterial infections observed during therapy were produced frequently by organisms which became numerically significant only after treatment was started.

Aureomycin and chloramphenicol were without effect in reducing the risk of secondary bacterial infections, when compared to control patients receiving no specific therapy. As a matter of fact, the number of complications occurring with aureomycin was greater than that in untreated patients. While the incidence of bronchopneumonia was reduced, there was an increase in suppurative otitis media when antibiotics were used. Of particular importance is the fact that many of these infections were due to organisms which rarely cause complications in untreated cases. In patients receiving no specific therapy, the Pneumococcus, beta-hemolytic Streptococcus and *H. influenzae* are the agents most commonly involved in secondary pneumonia while suppurative otitis media is due mainly to *Staph. aureus, Str. pyogenes,* the Pneumococcus, and *H. influenzae.* It is very striking, therefore, to note that middle ear infections were caused by *P. vulgaris* in the aureomycin-treated group and that chloramphenicol did not protect completely against invasion by either the Pneumoccoccus or the beta-hemolytic Streptococcus. The incidence of complications was lowest with terramycin, although one case of bronchopneumonia and two of acute monilial stomatopharyngitis were observed in the children receiving this drug.

These observations suggest the use of antibiotics for prophylaxis in whooping cough. Although terramycin was found to be active in this respect, it did not eliminate compli-

cations completely. In the final analysis, reduction of the mortality rate to as close to zero as possible in very young children with pertussis is the ultimate objective. That this was *not* accomplished to a greater degree in patients given specific therapy than in those in whom the primary disease was not treated is borne out by the following experience: There was one death in the group receiving chemotherapy; this occurred in a 3-month-old child and was due to encephalopathy and obstruction of the entire bronchial tree by thick mucus. In 425 patients cared for at the Haynes Memorial Hospital between 1945 and 1950, none of whom received any antibiotic unless a secondary bacterial infection supervened, there were two deaths, 0.44 per cent. Both of these were in children less than 6 months old; one resulted from occlusion of the bronchial tree and the other from a massive cerebral hemorrhage. These are accidents that probably cannot be prevented by chemoprophylaxis; no deaths resulted from secondary bacterial infection in either the treated or untreated patients. Although serious complications of this type have occurred in both groups, their early recognition and intensive treatment have eliminated them as causes of death. Chemotherapy may result in superinfections with organisms such as *P. vulgaris* which are difficult to treat in many instances with the antibiotics that are available today. Attempts at prophylaxis, therefore, may lead to a situation more difficult to manage than if the patient were given no treatment because the bacteria which commonly produce secondary infections in untreated children—Pneumococcus, Streptococcus, *H. influenzae*—are highly susceptible to chemotherapy.

CONCLUSIONS

1. Aureomycin, chloramphenicol, and terramycin have little or no effect in reducing the frequency or severity of coughing in the paroxysmal phase of pertussis.

2. Aureomycin and chloramphenicol are about equally effective in eradicating *H. pertussis* from the respiratory tract but terramycin is the most effective of the drugs in this respect.

3. All of the antibiotics produce important changes in the bacterial flora of the nasopharynx. Proteus, *E. coli*, and *A. aerogenes* were found most commonly when aureomycin was used. Chloramphenicol did not prevent the appearance of the Pneumococcus in the upper respiratory tract during the period of therapy.

4. The incidence of secondary bacterial infections in pertussis is not reduced appreciably by either aureomycin or chloramphenicol. Terramycin is the agent most effective in decreasing the risk of complications.

5. Wide application of the chemotherapeutic agents now available for control of the paroxysms in pertussis does not seem warranted.

6. Aureomycin and chloramphenicol do not appear to prevent secondary bacterial infections in whooping cough. If prophylaxis is attempted, terramycin, although not completely satisfactory, is the preferred drug.

7. The treatment of choice for pertussis is good nursing care, maintenance of adequate nutrition, hydration and electrolyte balance, and the recognition and early, intensive treatment of complications.

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CITROVORUM FACTOR IN LEUCEMIA

Two Cases With Autopsy Findings

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THE suppression of toxic manifestations of aminopterin and amethopterin used in the therapy of metastatic neoplasm by the "citrovorum factor"[1] has been reported by Schoenbach and associates.[2] The experimental use of folic acid in preventing but not reversing the toxic effects of the antifolic acid compounds has been reported by Greenspan and collaborators,[3] and Goldin and co-workers.[4] Burchenal and associates[5] suppressed the toxic effects of the antifolic acid compounds with citrovorum in experimental animals.

Two cases of leucemia are reported: a patient with lymphatic leucemia treated with 0.5 to 1 mg. of aminopterin daily and a patient with acute myelogenous leucemia treated with 5 mg. of amethopterin daily. The two patients developed toxic manifestations, which were ulcerations of the palate and oral mucosa, gastrointestinal discomfort, and hemorrhage. These toxic effects were suppressed temporarily in both cases with citrovorum (Fig. 1).

CASE REPORTS

Case 1.—H. D. (916-50 B), 5-year-old white male, had been discharged from the Arkansas Children's Hospital four months prior (June 15, 1950) to the onset of his leucemia after receiving a course of penicillin for the treatment of osteomyelitis. Two days before the second admission (Oct. 10, 1950) the mother noticed the development of multiple small bruises over the body, irritability, and lethargy. He was brought to the hospital after the bruising phenomenon spread to the face. No other evidence of hemorrhage had been seen. The liver, spleen, and lymph glands were found to be enlarged and the blood count revealed hemoglobin 11 Gm., platelets 16,000, white blood cells 21,000, with 93 per cent lymphocytes in the differential. Bleeding, clotting, and prothrombin times were normal. Bone marrow examination confirmed the diagnosis of lymphocytic leucemia. An eighteen-day course of ACTH, 40 mg. daily in divided doses, was given but the patient did not respond, became febrile, with a progressive rise in the white blood count and a fall in the hemoglobin. Immediately after stopping ACTH, a seventeen-day course of cortisone, 200 mg. statim intramuscularly and 100 mg. daily orally was given. Improvement was noted in general condition but there was no change in the blood findings. The patient was discharged on prophylactic doses of aureomycin and followed in the out-patient clinic. Then the hemoglobin was 12.5 Gm., and the white blood count was 16,000 with 89 per cent lymphocytes.

When readmitted six weeks later (Jan. 24, 1951), the patient had multiple ecchymotic areas on the body, the white blood count was 181,600 with 96 per cent lymphocytes; there were 4,000 platelets, and the hemoglobin was 8.5 Gm. Aminopterin 0.5 mg. was given intramuscularly for one day and 1 mg.

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The citrovorum (Leucovorin, synthetic) was supplied by the Lederle Laboratories Division American Cyanamid Company, Pearl River, N. Y.

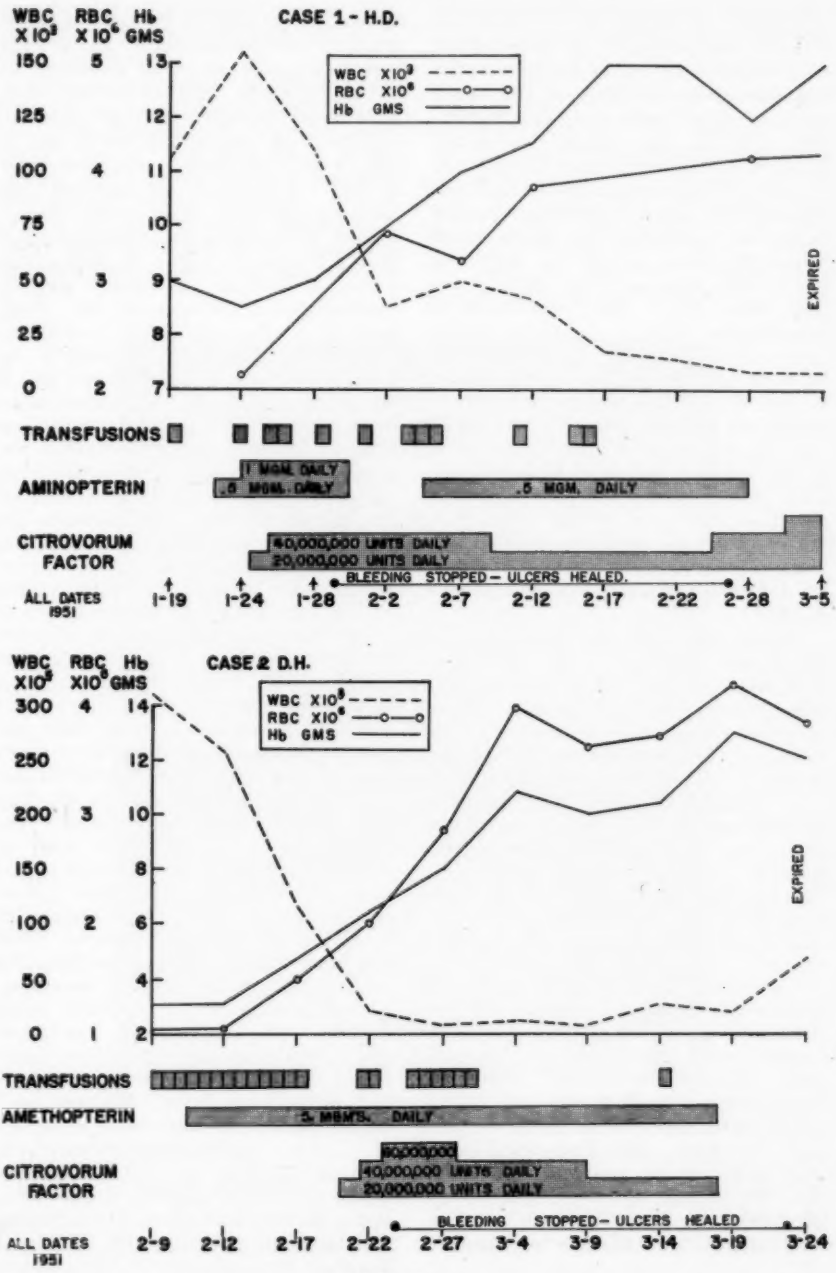

WBC X10³
RBC X10⁶
Hb GMS
CASE 1 - H.D.
150 5 13
125 12
100 4 11
75 10
50 3 9
25 8
0 2 7
WBC X10³
RBC X10⁶
Hb GMS
EXPIRED
TRANSFUSIONS
AMINOPTERIN
1 MGM. DAILY
.5 MGM. DAILY
.5 MGM. DAILY
CITROVORUM FACTOR
40,000,000 UNITS DAILY
20,000,000 UNITS DAILY
BLEEDING STOPPED – ULCERS HEALED.
ALL DATES 1951
1-19 1-24 1-28 2-2 2-7 2-12 2-17 2-22 2-28 3-5
WBC X10³
RBC X10⁶
Hb GMS
CASE 2 D.H.
300 4 14
250 12
200 3 10
150 8
100 2 6
50 4
0 1 2
WBC X10³
RBC X10⁶
Hb GMS
EXPIRED
TRANSFUSIONS
AMETHOPTERIN
5 MGMS. DAILY
80,000,000
40,000,000 UNITS DAILY
20,000,000 UNITS DAILY
BLEEDING STOPPED – ULCERS HEALED
ALL DATES 1951
2-9 2-12 2-17 2-22 2-27 3-4 3-9 3-14 3-19 3-24

Fig. 1.

given each day thereafter. Ulcerations of the mouth and gastrointestinal hemorrhages ensued on the fourth day and citrovorum was started, 10,000,000 units (0.5 c.c.) once and then 20,000,000 units (1 c.c.) daily, thereafter. Five days after starting citrovorum, the buccal membrane ulcerations had cleared and gastrointestinal hemorrhage had ceased. The white blood count fell from 181,000 to 18,000 in twenty-two days and to 8,200 by the thirty-fifth day. The proportion of lymphocytes, however, continued at the same high level. The platelets ranged between 4,000 to 10,000. On the thirty-second day of treatment, the patient developed a very diffuse eruption of chicken pox which within a matter of hours became severely hemorrhagic. The patient again manifested bloody vomitus and melena, and the citrovorum dose was increased. The patient went rapidly downhill, and expired on the forty-first day of treatment (March 5, 1951).

Autopsy by Dr. W. S. Orr.—The significant findings on autopsy were: numerous large hemorrhagic areas present over the entire surface of the body, showing some crustation; they averaged from 5 to 20 mm. in diameter. Many showed exudation of blood from the surface. There were petechial hemorrhages in the heart, lungs, spleen, pancreas, gastrointestinal tract and kidneys, with leucemic infiltration. The bone marrow showed leucemic cells slightly less profuse than previously; the platelets were reduced in number.

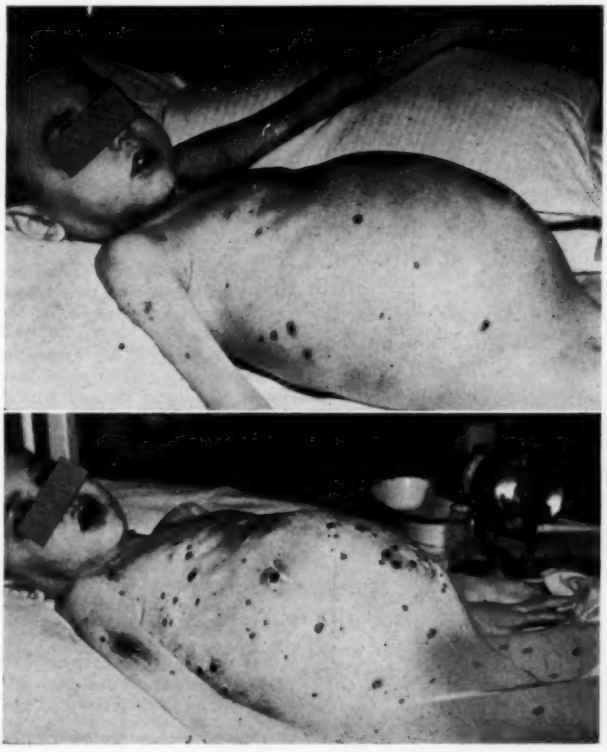
CASE 2.—D. H. (79151 A),* 14-month-old white male, became ill, four months before death, with an acute upper respiratory infection. Abdominal enlargement and periorbital hemorrhage were first noted about one month after onset of the upper respiratory infection. The first blood count was obtained by the local physician and the patient admitted to a private hospital (Jan. 1, 1951), with the diagnosis of acute myelogenous leucemia, which was confirmed by bone marrow studies. Eighteen days of ACTH treatment were given in a dosage of 50 mg. daily in divided doses. Multiple blood transfusions were given to maintain the hemoglobin above the 11 Gm. level. No benefit was seen from ACTH. Approximately two and one-half months after onset of the illness, he was admitted to the Arkansas Children's Hospital on Feb. 9, 1951. The white blood count was 335,000 and the predominating cell a myelocyte. Bone marrow studies confirmed the diagnosis; the platelets were moderately reduced in number. Amethopterin, 5 mg. daily, and daily blood transfusions were begun but were unavailing, as massive hematemesis and melena ensued. There were, also, periorbital hemorrhages and bleeding lesions of the buccal mucosa. Transfusions did not maintain the hemoglobin level and thirteen days after admission, citrovorum was started, 10,000,000 units on the first day which was increased to 10,000,000 units every twelve hours on the second day, and this was further increased to 20,000,000 units every eight hours on the third day. This dose was maintained for six days and then reduced. Four days after starting the citrovorum, the gastrointestinal bleeding had stopped and in six days the mouth lesions had cleared. The hemoglobin levels began to stay up without transfusion and showed a progressive rise. On the eleventh hospital day the white blood count fell from 335,000 on admission to 9,400. The bone marrow showed less leucemic infiltration and the platelets were about as numerous as at the previous examination. The patient was discharged and followed in the out-patient clinic, where he was given the amethopterin and citrovorum daily. He was readmitted nine days later with an attack of acute laryngotracheobronchitis. The hemoglobin was 13.5 Gm., red blood count 4.4 million, white blood count 34,800, and there was no manifest bleeding tendency. On the second hospital day (March 23), the patient expectorated a small amount of blood

*Courtesy Dr. Sam Phillips, Little Rock, Ark.

and developed hematuria. He expired suddenly. Citrovorum was not available at this time.

Autopsy.—Autopsy findings were limited to petechial hemorrhages in the cornea, conjunctiva, buccal mucosa, heart, lungs, gastrointestinal tract, spleen, and kidneys, with microscopic findings of diffuse leucemic infiltrations. The bone marrow showed moderate leucemic infiltration and the platelets were slightly reduced in number.

doses of 40,000,000 units in Case 1 and in doses of 40,000,000 to 60,000,000 units in Case 2, in from four to six days. Regression of the ulcers was noted in Case 1 on the fifth day and in Case 2 on the fourth day after starting citrovorum. The melena ceased in Case 1 on the fifth day and the profuse melena in Case 2 was noticeably less severe on the fourth day and had stopped entirely by the sixth day. The



A.

B.

Fig. 2. (Case 1).—*A*, First day of chicken pox. *B*, Ninth day of chicken pox.

DISCUSSION

In these two cases of leucemia, it was our impression that citrovorum appeared to suppress the toxic effects of aminopterin and amethopterin in daily transfusions were continued until the hemoglobin was between 10 to 12 Gm.

Case 1, who had been exposed to chicken pox while in the hospital, developed the disease on the thirty-second

day of treatment. The lesions, which were clear at first, filled with hemorrhage in a few hours (Fig. 2). The dosage of citrovorum was increased but did not affect the hemorrhage into the new crops of lesions, and as they spread to the extremities and face, small amounts of blood were noted in the stools which increased in amounts. The ulcers on the hard palate and lips, which were healed, again broke down. The course terminated fatally on the forty-first day of treatment and on the ninth day of chicken pox.

Case 2 did not show any more bleeding tendencies nor ulcerations of buccal mucosa after the citrovorum was started. After being discharged to his home, he was followed in the out-patient clinic where he continued to receive amethopterin, 5 mg. daily, and 20,000,000 units daily of citrovorum for four more days. He was readmitted because of acute laryngotracheobronchitis, and on this admission he suddenly expired on the second hospital day. On both cases aminopterin and amethopterin were continued throughout the period when toxic manifestations were present. The aminopterin in Case 1 was stopped for a six-day period which was after some of its toxic effects had subsided.

In view of a previous report,[5] we feel that while citrovorum antagonized the thrombocytopenia due to the antifolic drugs, the same result would have been attained by reducing the dosage of the antifolic acid drugs.

SUMMARY

1. The clinical and autopsy findings are reported in two cases of leucemia, one acute lymphatic and the other acute myelogenous leucemia.

2. The toxic effects of aminopterin and amethopterin were temporarily suppressed by the use of citrovorum.

3. In Case 1, in which hemorrhagic lesions developed in chicken pox, the citrovorum did not prevent the return of the toxic manifestations of aminopterin. The dosage may have been too small.

4. It is felt that the effects of the citrovorum factor were due to a general inhibition of the antifolic acid compounds.

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NUMMULAR ECZEMA IN CHILDREN

Report of Six Cases

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ONE of the many bizarre clinical variants of atopic dermatitis seen among infants and children is that form which, for the lack of a better term, is referred to as "nummular eczema." Atopic dermatitis in infants and children assumes different clinical expressions. The usual type is that which in its acute stage is characterized by the presence of well-defined plaques of erythematous papules with exudation (edema) and which progresses to vesiculation. Under favorable conditions, the cessation of the oozing indicates that edema is subsiding. The dried crust then falls away, scaling follows, and the inflamed skin returns to a normal state. When the primary dermatosis becomes complicated by secondary infection, as from scratching, the atopic dermatitis is said to be impetiginized or pyodermized. Chronic atopic dermatitis, in contrast to the acute phase, is recognized by lesions that are dry and leathery, and the term "lichenification" is applied to these to indicate that the linear markings of the skin at the site of the plaques stand out prominently. In the chronic stage of atopic dermatitis there is little edema, at least clinically. Between the acute and chronic stages one finds all possible variations, as an acute episode superimposed upon the chronic lesions.

From the Out-Patient Pediatric Dermatologic Clinic of the Skin and Cancer Hospital, Dr. Carroll S. Wright, Medical Director, Temple University Hospital Service.

Patient T. S. J. was presented before the Philadelphia Dermatological Society, Feb. 23, 1951.

CLASSIFICATION

The distribution of the lesions in the classical type of atopic dermatitis is usually upon the antecubital and popliteal areas, and the face and neck. Other types of eczema of interest to pediatricians include intertriginous eczema, contact eczema, seborrheic eczema, infectious eczematoid dermatitis, and dermatophytosis. All of these special varieties are characterized histopathologically by edema of the epidermis, or of the corium, or of both, although the etiological factors vary widely in each case. Thus, intertriginous eczema is a dermatitis produced by moisture, friction, and poor hygiene, and usually occurs upon the folds of the skin, on the groins, or underneath the breasts in older children and in the axilla. In the simple inflammatory state, this condition is spoken of as an intertriginous dermatitis or intertrigo. When it becomes eczematized, the condition is known as an intertriginous eczema.

By a contact dermatitis is meant as eczematoid dermatitis caused by sensitization to some external substance. This entity should not be confused with dermatitis medicamentosa due to some drug taken internally. Dermatitis venenata is a broad term including both contact and occupational eczemas. Examples of contact eczema are ivy, rhus, and sumac poisoning, and those produced by contact with dyed materials as dyed socks and underwear, and

from handling chemicals. Clinically, this type of eczema is recognized by extreme erythema, edema, and vesiculation. Histopathologically, its features are similar to those of atopic dermatitis, with the addition of a vesicle or series of vesicles which are seen in the epidermis.

Eczema seborrheicum (seborrheic eczema) is a form of eczema thought to be caused by a microscopic organism although no actual proof exists that such is the case. The theory is that the individual becomes sensitized to an organism, the *Pityrosporum ovale*. Sometimes, too, the term seborrhea is used for seborrheic dermatitis with confusing result. Some dermatologists prefer to prefix the term "noninflammatory" to describe the type where seborrhea occurs without eczematization. Others use the expression "seborrheic dermatitis" to indicate an inflammatory dermatosis. Seborrhea sicca is a dry dandruff, while seborrhea steatodes refers to the waxy type of seborrhea. The French school describes both types as Pityriasis, after the French term for scale.

Dermatitis infectiosum eczematoides (infectious eczematoid dermatitis), first described by Fordyce of New York, and by Engman of St. Louis, independently, is a secondary eczema usually induced by an exudate upon any part of the body from any cause. Examples are found in boils, abscesses, draining sinuses, a discharging ear, or leg ulcers, where the exudate involves uninfected areas of the skin. By spreading peripherally, the exudate, serving to sensitize the patient, results in the so-called "infectious eczematoid dermatitis."

The term "dermatophytosis," coined by Highman of New York, refers to an eczematoid eruption caused by superficial fungi. Here, too, the lesions are frequently exudative and histopathologic study of the skin discloses an eczema-like reaction of the epidermis.

NUMMULAR ECZEMA

Of particular interest to pediatricians and to dermatologists is the dermatosis known as eczema nummularis (nummular eczema) wherein the individual lesions are definitely marginated, oval or rounded, and as the name "nummular" signifies, coinlike, of the size of a ten-cent piece, or larger, of a quarter or a half dollar. The lesions show a predilection for the dorsal surfaces of the hands, wrists, and forearms, but may occur anywhere on the body. They occur in adults as well as in children, and are definitely eczematoid. They are sometimes referred to as a "mycotic eczema." The etiology of the complaint is poorly understood, although most dermatologists classify it as an eczema. Hill[1] states that nummular eczema is not very uncommon in infants 1 to 2 years of age, and adds that it probably has nothing to do with allergy, although by those who are not familiar with it, it is usually mistaken for atopic dermatitis. However, in the cases to be reported, a definite history of allergy was obtained in five children.

Sachs and associates,[2] in a discussion of the "Histopathology of Eczematoid Dermatoses," report their belief that nummular eczema is more of a neurodermatitis than an eczema. These investigators state that "little has been written on the pathology of this disease. It is often clinically confounded with other dermatoses, as fungus infections, contact dermatitis, and even dermatitis herpetiformis. The path-

ologic features of this disease appear to be chiefly those of neurodermatitis plus an epidermic vesicle. The cutis and epidermis are similar to neurodermatitis. In addition, there is the intraepidermic vesicle or vesicles about which there is little or no edema (similar to the contact vesicle)." According to this description, nummular eczema has the same histopathologic pattern as neurodermatitis with the addition of an intraepidermic vesicle. Nevertheless this vesicle could not be demonstrated in any of our carefully studied sections. Accordingly, it would seem in the light of the otherwise similar histopathologic picture displayed in these cases, that a vesicle is not absolutely essential for the histopathologic diagnosis of nummular eczema.

Lever[3] classifies nummular eczema with infectious eczematoid dermatitis. He states (pp. 56, 57) that "nummular eczema is probably caused by a temporary loss of resistance in the skin to the ordinary bacterial flora of the skin, presents fairly sharply demarcated patches of erythema studded with discrete 'pin-point' vesicles or 'pinpoint erosions.'" The term "nummular eczema" itself was coined, it should be noted, by Devergie.[4] It is worth while referring to Devergie's original description in order to discover what this dermatologist meant by the term "nummular eczema." Devergie said, "Eczema nummularis has as its special feature the fact that it develops mainly on the surface of the limbs, particularly the upper extremities, though also the surface of the trunk; it appears in little patches which assume at once their full size; they are round, of a size of a five-franc piece or a little larger; they have no raised border—which distinguishes them from ringworm—their margin is flat and merges into the rest of the skin as an ordinary eczema; they are accompanied furthermore by redness, vesiculation, itching, and a serous secretion."

Clinical Signs.—Hill's account[5] describes nummular eczema with such clarity, exactness, and completeness as to make a classic account:

"The patches of nummular eczema are more regular in outline than those of atopic dermatitis, there is a sharper line of demarcation between the diseased and healthy skin, the larger ones are more 'boggy' and exudative and there is no lichenification. Itching may be almost absent or moderate: there is never the terrific itching such as in atopic dermatitis. The skin, except for the scanty numerous circumscribed patches, is smooth and of good quality. The scalp is not involved. Nothing whatever is known of the etiology of this dermatosis. As far as is known it has nothing to do with allergy. I have seen no patient with nummular eczema who had positive skin tests."

When one studies the histologic picture as described by Pollitzer,[4] he finds that it resembles that of eczema. Under histology (p. 720), Pollitzer states "A comparison of the histologic picture with that of eczema shows marked differences, which, however, it must be admitted are mainly those of degree. The vesicle viewed by itself greatly resembles a vesicle of eczema, but in eczema the vesicle is only the pathologic expression of the acme of a process which involves the entire epidermis, while in the disease I have described there are virtually no changes in the epidermis in the intervesicular portions. The entire picture makes the impression of a process whose primary

seat anatomically is in the blood vessels of the subpapillary layers, the vesicle formation resulting from the sudden pouring out of serum from the capillaries of a simple papillae."

Apparently Pollitzer's experience with nummular eczema was not very extensive, especially with children, since he states, "The disease is not seasonal, it occurs at all periods of the year. I have never seen it in children nor in the aged; my cases range from 18 to 47 years of age." As to frequency, again he states, "I have seen four or five cases or more in a year."

Fig. 1 (Case 1).—T. S. J., aged 4 years. Note several demarcated discoid lesions consisting of pin-point vesicles upon an elevated erythematous base upon the lower extremities.

CASE REPORTS

CASE 1.—T. S. J., a 4-year-old white male child, was first seen in the pediatric out-patient dermatology department at the Skin and Cancer Hospital, Jan. 26, 1951, for an eruption located upon the extensor surfaces of the lower extremities. The eruption had been present since August, 1950, and had been better and worse from time to time. Occasionally the lesions were characterized by "oozing," especially after their being irritated by scratching. The child had had measles, mumps, and whooping cough without sequelae. He had received the usual immunologic procedures and was vaccinated against smallpox. His paternal uncle had asthma. A sister of the patient was said to have had some kind of "skin trouble," but the exact nature of this could not be determined by interrogating the mother. Otherwise, the past history was irrelevant to the present report. Examination of the child's skin disclosed several dis-

crete, sharply demarcated, dry, scaly, papulosquamous lesions upon the extensor surfaces of both lower extremities, each measuring from 1 to 5 cm. in diameter. A similar lesion measuring 1 cm. in diameter was seen upon the extensor surface of the left elbow, while several papules of pea size were found upon the buttocks. When one of the lesions was gently scraped by means of a penny, bleeding points appeared. The physical examination was negative.

Treatment consisted in the topical use of a 1 per cent ichthammol, 1 per cent salicylic acid in Aquaphor.* Later, this prescription was replaced by a Supertah Ointment.† Improvement followed.

CASE 2.—S. M., a 25-month-old white male child, was first seen in the outpatient dermatology department of the Skin and Cancer Hospital, Jan. 1, 1951. The patient had been brought to the hospital for an itching rash located

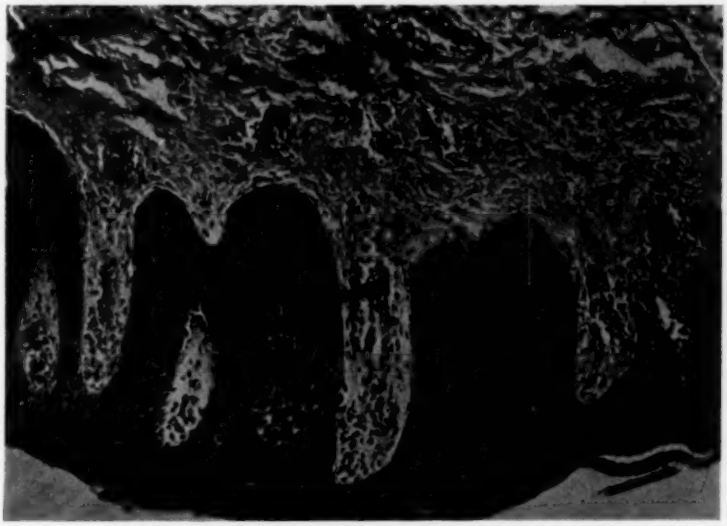

Fig. 2 (Case 1).—Histopathologic section. Note the combined histopathologic picture of neurodermatitis and psoriasis. The club-shaped acanthosis and bihorned acanthosis of the rete pegs, and dilatation of the blood capillaries high up in the papillary bodies are in favor of psoriasis. The uniform small round cell and histiocytic infiltrate of the upper portion of the corium and pale-staining epidermis are in favor of neurodermatitis. Diagnosis—psoriasiform neurodermatitis.

A biopsy of one of the skin lesions, taken February 8, was reported as follows: "Papillary hyperplasia of the lining epithelium, slight hyperkeratosis and parakeratosis. The corium pegs are rather prominent, extending close to the surface epithelium with tendency toward ulceration and showing capillary hyperplasia and ser-cellular exudate. The rest of the section shows lymphocytic infiltration, slight congestion and granulation tissue, fibrosis and slight necrosis. Conclusion—Psoriasiform dermatitis."

upon the left calf, right popliteal region, and both antecubital areas. The rash had been present for three months, and was characterized by "oozing" at times, but for the most part was dry. The child had been vaccinated against smallpox and had received immunization against diphtheria, pertussis, and tetanus. The infant had been bottle fed since birth, had no aversion to foods, and showed no other allergies. Nor did any of the members of his

*Duke Laboratories, Inc., Stamford, Conn.
†Tailby-Nason Company, Cambridge, Mass.

family give a positive allergic history. The past history was otherwise irrelevant.

Examination disclosed numerous erythematous papules and some crusts as well as several papulosquamous discoid plaques, located upon the left calf and the right popliteal region. Both antecubital areas showed the thickened, lichenified plaques, characteristic of atopic dermatitis. Several discrete papules were also seen upon the forehead and upon the cheeks. The tentative diagnosis was of atopic dermatitis. A biopsy of the lesion of the calf on February 28 was reported as follows: "Papillary hyperplasia of the lining epithelium, hyperkeratosis and parakeratosis. The corionic pegs are rather prominent extending close to the surface epithelium with a tendency toward ulceration and showing capillary hyperplasia and ser-cellular exudates; slight congestion, granulation tissue, fibrosis and slight necrosis. Conclusion—Psoriasiform dermatitis."

Treatment consisted in the use of wet dressings during the exudative stage, the use of pHsioderm (instead of ordinary soap) and teaspoonful doses of Benadryl elixir three times daily. A 1 per cent ichthamnol in equal parts of zinc oxide paste N. F. and rose water ointment was ordered topically, to be applied three times daily. On one occasion, the patient received 50,000 units of Duracillin intramuscularly. The condition improved but recurred.

CASE 3.—L. W., a 4-year-old white female child, was first seen by one of us (H. H. P.) on March 23, 1951, because of a single circinate papulosquamous lesion located upon the dorsum of the right wrist. Because of its circinate appearance, the mother thought the lesion might be ringworm. However, she also believed that exposure to outdoor weather might have played a part in the occurrence. The lesion had been first noticed five weeks prior to the time the child was brought to the office. A definite history of allergy was obtained. The father has an allergic rhinitis and has been under the care of an otolaryngologist for several years. The child is definitely allergic to ragweed pollens and has experienced episodes of repeated sneezing which begin in the late summer and continue until the first frost. She has received treatment for hay fever from an allergist. The patient, an only child, was a healthy bottle-fed infant and had received the usual immunologic procedures during infancy, including vaccination against smallpox. Otherwise, the past history is unimportant. There were no gastrointestinal allergies. Upon examination, a single definitely demarcated circinate, somewhat whitish, elevated lesion, measuring less in diameter than a ten-cent piece, was seen upon the skin overlying the dorsal area of the left wrist. Itching was variable.

Treatment consisted in the topical application of 1 per cent ichthammol in an ointment base consisting of equal parts of rose water ointment and zinc oxide ointment, applied three times daily. A superoilated soap (Oilatum Soap, unscented*) was ordered instead of ordinary soap. Improvement followed.

CASE 4.—A. B., a 2½-year-old white male child, was seen at the Skin and Cancer Hospital on Feb. 18, 1947, for a vesicular eruption of the arms and legs. The eruption, which had been present for eight months prior to the child's first examination, was characterized by several sharply circumscribed vesicular lesions measuring from 1 to 3 cm. in diameter. The lesions upon the left ankle were more confluent than those upon the other areas. The dermatosis first appeared in the summer of 1946, when the subject was 2 years old, upon the left ankle; four months later it spread to the right ankle and right calf, also to the left and right arms. These lesions were accompanied by severe itching and appeared worse. The infant had been born prematurely (seven months' pregnancy), had been artificially fed but had thrived nicely throughout infancy. He had received immunization

*Stiefel Medicinal Soaps, Oak Hill, N. Y.

against diphtheria, whooping cough, and was vaccinated for smallpox. There were no illnesses. The mother believed that his food did not play any part in the etiology of the eruption. His paternal cousin has rose fever. Examination disclosed a healthy child, without abnormalities or physical defects. A diagnosis or nummular eczema was made. Wet dressings of German chamomile flowers were prescribed for the edematous stage and followed by a 1 per cent of oil of cade in an ointment base consisting of 10 parts of Burow's solution, 20 parts of anhydrous lanolin, and 30 parts of Lassar's zinc paste without salicylic acid. The lesions healed rapidly at the end of one month. When the child was seen a month later, there had been no recurrence.

Examination disclosed a healthy infant. She had had the usual immunologic injections and was vaccinated against smallpox. She has had no infectious diseases up to the present time. The father had eczema when he was a baby. The child received a well-balanced diet with adequate vitamins A, C, and D.

Treatment consisted in the topical application of a 2 per cent oil of cade (juniper tar) in a zinc oxide ointment, the use of a ½ gr. phenobarbital tablet before bedtime, and of a hyperoilated soap (Oilatum Soap, unscented) instead of ordinary soap. Upon this local medication, the lesion involuted almost completely within six days. However, two days later, after the patient participated in a birthday party, at which she consumed considerable chocolate,

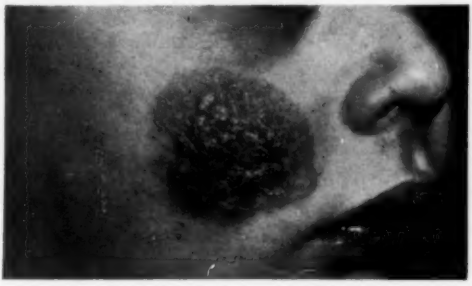

Fig. 3 (Case 5).—J. B., aged 2 years. Nummular eczema localized to right side of the face. The area measured 3¼ cm. from above downward and from side to side. The lesion was characterized by a definitely demarcated elevated area and erythematous oozing scales. Improvement followed a 2 per cent oil of cade (juniper tar U.S.P.) in zinc oxide ointment.

Case 5.—J. B., a 2-year-old white female child, was referred to one of us (H. H. P.) by Dr. L. Kacher, March 7, 1951, because of a single elevated patch on the right side of the face. The condition began in December, 1950, as tiny pin-point vesicles which gradually enlarged until at present it is 3¼ by 3¼ cm. The character is scaly, somewhat heaped-up, a definitely circumscribed plaque, which oozes occasionally, especially after being scratched and which at times is covered by simple crusts. Apart from a small verruca seen upon the palmar surface of the right hand the patient exhibits no other skin lesions.

candy, and cake, a slight recurrence of the lesion appeared. Upon resumption of the application of the oil of cade ointment, complete disappearance of the lesion again followed.

Case 6.—E. A. G., a 1-year-old white male infant, was seen on April 27, 1951, for a single elevated plaque upon the dorsal aspect of the right leg. The lesion started when the child was aged 4 months as an erythematous vesicular sharply demarcated nummular lesion about the size of a quarter piece, which gradually grew larger until it attained the present dimension of 2 by 5 cm. At times the dermatosis oozes, at other

times the affected area of the skin is quite dry and scaly and is covered by crust.

The infant has been vaccinated and to date has received immunization against diphtheria. He has been a healthy infant since birth, bottle fed, and has four teeth. He has received adequate doses of vitamins A, C, and D. His maternal aunt had eczema as a child. There is no evidence of any other allergy in the family, either in the immediate family or remotely related. Examination disclosed a large, nummular lesion about the size of a dollar, sharply marginated, and consisting of numerous vesicles with edematous fluid upon an erythematous base. Treatment consisted of wet dressings of chamomile tea for the first forty-eight hours, which was then followed by ¼ per cent oil of cade in a zinc oxide ointment base. Improvement followed after one week of topical therapy.

Fig. 4 (Case 6).—E. A. G., aged 1 year. Note the acute exudative nummular lesions upon the dorsal aspect of the right leg. Several satellite lesions may also be seen immediately beneath the large nummular lesion.

MANAGEMENT

It is generally agreed that so-called nummular eczema responds satisfactorily to one of the tars. Oil of cade (juniper tar U.S.P.) is a favorite remedy among many dermatologists. Our patients responded favorably to a 1 per cent ichthammol or another tar in an ointment base consisting of equal parts of rose water ointment (without the rose oil) and zinc oxide paste (without salicylic acid). Hill states that he has had fair therapeutic results by painting each lesion with crude coal tar once a day. Further, according to Hill, no change in diet is necessary. Also, the lesions respond to small doses of roentgen therapy. However, x-rays were not found necessary in any of the cases reported here.

In general, the plan of management for nummular eczema is similar to that for atopic dermatitis. Wet dressings are indicated during the acute exudative stage, and mild tar preparations during the chronic recalcitrant stage. We are particularly fond of wet dressings of chamomile tea during the first twenty-four to seventy-two hours of the dermatosis when the lesions are wet with weeping. Their choice of preparation during the third stage, that is, the chronic stage, when the lesions have become thickened, scaly and leathery, is ichthammol or oil of cade in a 1 to 2 per cent preferably in a rose water ointment, combined with an equal quantity of Lassar's simple paste. On the other hand, the antihistamines per

os have proved disappointing in their hands for relieving the pruritus.

COMMENT

When patient T. S. J. was first seen, the scraping of one of the lesions with the edge of a copper penny produced the so-called "Auspitz phenomenon." However, the lesions still were not thought to be those of psoriasis, in spite of the bleeding points, because they lacked the characteristic "mother-of-pearl" silvery scale characteristic of psoriasis. Too, the "Auspitz phenomenon" (bleeding points) is not restricted to psoriasis alone, but also occurs in other dermatoses, such as neurodermatitis, chronic discoid lichenoid eczematoid dermatitis (never seen in children). The histopathologic picture is of interest in this connection; it showed an histologic pattern resembling both psoriasis and neurodermatitis. The rete pegs (rete malpighii) showed a club-shaped acanthosis. Further, one of the rete pegs disclosed the "hornlike" character which has been stressed by Darier and others as characteristic of the histopathologic diagnosis of psoriasis. Also in favor of the diagnosis of psoriasis are many dilated superficial blood capillaries situated high up in the papillary bodies; also parakeratosis. (Incidentally, the latter accounts for the scales of the lesions.) However, against the diagnosis of psoriasis counts the presence of a well-defined granular layer which remained intact throughout the entire section examined. This is seldom, if ever, seen in the picture of true psoriasis. A definite focal infiltrate consisting of small round cells and wandering connective tissue cells (histiocytes) appeared to encircle the blood vessels; and this latter is a characteristic finding in neurodermatitis (atopic dermatitis). In addition, the cellular infiltrate seen throughout the upper corium (papillary bodies) is quite uniform, and in keeping with the picture of neurodermatitis. Further, upon close examination one finds that the thinning of the papillary plates, characteristic of psoriasis, is absent, and that there exists no evidence of a Sabouraud abscess (Monro abscess) in the epidermis. It must be admitted, however, that a Sabouraud abscess is not absolutely necessary for the histopathologic diagnosis of psoriasis. On the other hand, in five reported patients (T. S. J., L. W., A. B., J. B., and E. A. G.) a definite history of allergy was elicited either in the patient or in closely related members of the family.

Careful studies have established that in children subject to atopic dermatitis, a positive history of allergy in other members of the family occurs in from 40 to 60 per cent of instances. The histopathologic picture of the biopsy both in T. S. J. and in L. W. indicates that there is interstitial edema of the epidermis characterized by pale-staining effect of the tissue, another characteristic in atopic dermatitis and neurodermatitis. So it is that, relying upon the histopathologic picture, one seems justified in concluding that the microscopic pattern conforms to that entity, the so-called "psoriasiform neurodermatitis" (sometimes referred to as "psoriasiform eczema" and diagnosed as "psoriasiform dermatitis" by the pathologists) rather than to a true psoriasis. We wish to emphasize our preference for the terminology "psoriasiform neurodermatitis" over "psoriasiform eczema" or "psoriasiform dermatitis." In any case, the term eczema is a bad one since it is used

rather too loosely by the average physician to indicate many unrelated dermatoses, whereas the dermatologist understands by it a definite histopathologic pattern which accords with the microscopic picture of a true atopic dermatitis, a neurodermatitis (in later life), or a contact dermatitis (eczematoid). For the same reason, it might be better to describe the histopathologic picture as that of a "psoriasiform neurodermatitis" than as "psoriasiform dermatitis" because of the definite histopathologic findings of neurodermatitis (uniform infiltrate throughout the papillary bodies, infiltrate surrounding the blood vessels, with hypergranulosis and edema of the epidermis and corium) modified somewhat by the coincidental findings of psoriasis (pseudopsoriasis-club-shaped acanthosis of the rete pegs, parakeratosis, dilated blood vessels in the papillary bodies, etc.).

From the clinical findings and the histopathology it appears that the so-called nummular eczema may assume different forms depending upon the extent of the pathologic picture. It is our feeling that the condition is relatively more common than has been heretofore believed, and that alertness in looking for it will disclose that the condition is common among children.

SUMMARY

Six patients, five children and one infant, the subjects of so-called nummular eczema, are reported. The youngest child was 1 year of age, the oldest 4 years. Five of these six patients gave a definite history of allergy. One patient illustrated an unusual location of the nummular lesion upon the right side of the face. The histologic picture in nummular eczema is variable, depending upon the duration of the eczematous condition. Clinically, nummular eczema is characterized by sharply defined discoid lesions or plaques consisting of pin-point vesicles which may resemble those of atopic dermatitis, of neurodermatitis, or even of dermatitis herpetiformis, as has been pointed out by Sachs and associates. In two of the reported patients the histopathologic picture was that of a psoriasiform neurodermatitis, a condition generally recalcitrant to topical therapy, with recurrence the rule.

We have found the tars, particularly the oil of cade, most useful for therapeusis. It is our feeling that nummular eczema is more common than is supposed, usually being overlooked in the routine dermatologic examination of infants and children. The fact that five reportable cases have come to hand in a comparatively short time offers proof that this dermatosis occurs fairly frequently.

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CONGENITAL ATRESIA OF THE BILE DUCTS ASSOCIATED WITH ERYTHROBLASTOSIS FETALIS

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INTRODUCTION

OBSTRUCTION of the biliary tract of all types occurring in the newborn child with erythroblastosis fetalis is not uncommon. The etiology of the obstruction in the cases reported usually falls into one of four categories: (1) a transitory obstructive phase occurring in erythroblastosis due to the presence of inspissated bile plugs in the extrahepatic biliary passages, (2) pigment stones causing obstruction of the extrahepatic ducts, (3) intrahepatic obstruction with cirrhosis of the liver and bile thrombi in the intercellular bile ducts, or (4) congenital atresia of the bile ducts. Actual atresia of the ducts accompanying erythroblastosis is an uncommon type of obstruction and the concommitant occurrence of these two conditions has caused some authors to theorize upon a possible etiological relationship existing between the congenital atresia and erythroblastosis.

The literature concerning this combination of conditions has been sparse and to our knowledge only five cases have been reported in four separate papers until the present time. The actual pathology of erythroblastosis with regard to liver cell damage and intra- and extrahepatic bile duct damage has not been extensively studied, but a few authors[7] have intimated that the actual liver damage is greater than heretofore reported. The pathology of extrahepatic biliary tract atresia has been well described,[4] and a comparison of the etiology of the two conditions can be made.

The suggestion by several authors that Rh antigen-antibody reactions or that organization and fibrosis of intra- and extrahepatic bile plugs may play a role in the development of atresia of the extrahepatic bile ducts[2] was of particular interest to us.

ETIOLOGY

The normal development of the biliary tract occurs in the early weeks of embryonic life and is produced as an outpouching of the foregut called the hepatic diverticulum. Arey[3] states that the common duct and the hepatic ducts develop from the elongating portion of the hepatic diverticulum which first appears in the three-millimeter fetus (three and a half weeks). At first the whole biliary passage tends to be solid. In a five-millimeter embryo (four weeks), the gall bladder is a solid cylinder which is carried away from the duodenum by the elongating common duct. A distinct stem becomes recognizable as the cystic duct; and at seven weeks, a lumen has been established throughout most of the tract. Bile is secreted in fetuses about twelve weeks old. A congenitally narrowed or

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solid condition of the gall bladder or of the chief ducts is a retention of the temporary embryonic occlusion by an arrest of development at this solid stage of biliary tract development. Various theories have been advanced to explain this arrest of development; notably, fetal peritonitis, congenital syphilis, and, more recently, embryonic cholangitis. None of these theories, however, has been completely satisfactory and the cause is not yet fully apparent.

The etiology of congenital atresia of the bile ducts when occurring in erythroblastosis has been discussed in previous papers. Skelton and Tovey[14] suggested that biliary tract obstruction in children with icterus gravis may take one of two forms: (1) blockage of one of the larger bile ducts with inspissated bile, or (2) conversion of the bile ducts into a fibrous cord. They postulated that the plugging of the canaliculi and ducts with bile thrombi in icterus gravis might in some cases be followed by organization of the thrombi thus leading to fibrosis of the intra- and extrahepatic ducts causing a condition of the ducts resembling congenital atresia. They cited two cases in which congenital atresia of the bile ducts and erythroblastosis were coexistent and adduced from these cases that in certain patients the "so-called congenital obliteration" of the bile ducts occurs as sequelae to icterus gravis neonatorum. In one of these cases, however, they questioned whether the fibrosis of the common duct could be attributed to organization of a plug of inspissated bile. This child died when 2 days old and they reasoned that since bile thrombi do not appear until extrauterine life, probably there was not sufficient time for fibrosis of these thrombi to occur, and, therefore, this particular case probably could not be explained satisfactorily on that hypothesis. Their second patient recovered following operation and no proof was given that there was any etiological relationship between these two conditions. A few cases were cited in which erythroblastosis and congenital atresia of the bile ducts occurred in different members of the same family and the assumption was made that the etiology of both conditions was the same.

In 1946 Lightwood and Bodian[7] reviewed all the four cases reported to date and added one of their own. They believed that none of these cases had been fully proved to be both erythroblastosis and congenital atresia of the bile ducts, and concluded from these cases that no direct etiological relationship had been proved beyond doubt, though some of the cases had been highly suggestive. At any rate, they concluded, Rh isoimmunization would not appear to be a major etiological factor in the pathogenesis of atresia of the bile ducts when they occur together.

DIFFERENTIAL DIAGNOSIS

The symptoms and signs of erythroblastosis and congenital atresia of the bile ducts are well known, and the differential diagnosis ordinarily may be quite easy; but when the two conditions occur at the same time, a composite picture results in which the separate features of each condition may be recognized.

The diagnostic features of erythroblastosis are as follows: Usually, the child is Rh positive; the mother's blood is Rh negative and contains anti-Rh agglutinins. The disease is suspected in the newborn infant by the golden yellow vernix caseosa and a

hypertrophied placenta. The child usually develops jaundice in the first few days of life and has hepatosplenomegaly. There may be marked anemia and an increased number of circulating erythroblasts in the peripheral blood. The Coombs test is positive. The urine usually contains bile and increased urobilinogen. The stool contains bile and the van den Bergh reaction of the blood is usually direct positive or diphasic.

Obstructive jaundice of the newborn infant appears at birth or shortly thereafter. Occasionally, it may be delayed but once it appears it never abates. The jaundice usually has a greenish tinge and the icterus index usually is very high. The stools are clay colored from birth but may later become yellow presumably due to the passage of bile through the bowel wall. The urine is dark and contains bile but no urobilinogen. The van den Bergh test is direct positive. The liver is large but usually the spleen is normal in size. There is rarely an anemia and the state of nutrition is usually good.

"Because erythroblastosis is associated with a very high mortality in the first few days or weeks of life, the chance of confusing it with malformations of the bile ducts becomes progressively less as the age of the baby increases." (Ladd.[5])

There have been some cases of erythroblastosis reported during the course of which an obstructive pattern developed which lasted for a few weeks to many months. In these cases, congenital atresia may be suspected. If the obstruction is complete and not intermittent, diagnosis may be made only by exploratory operation. Some of these cases have been proved to have been due to a plug of inspissated bile in the extrahepatic ducts (Alway and Platou[1]), and operation may cure the patient by dislodgment of the obstructive plug (Ladd and Gross[6]). If congenital atresia is found at operation, about 20 per cent can be corrected by anastomosing a bile-filled duct to the duodenum.

Another process which simulates obstructive jaundice and in which operation is not indicated is erythroblastosis in which the obstructive symptoms are due to hepatic cell damage and apparently the accumulation of bile thrombi in the intercellular bile canaliculi.[12] Lightwood and Bodian[7] showed in some of their cases at autopsy that intrahepatic obstruction due to liver cell damage had occurred and cause an obstructive jaundice as well as cirrhosis. Microscopic examination showed the cirrhosis, a normal bile duct epithelium, but also bile plugs in the intercellular bile canaliculi as well as small bile globules in the liver cells.

REVIEW OF THE LITERATURE

The literature contains only five cases that we could find in which congenital atresia was believed to exist in a case of erythroblastosis (Table I). Some of the cases, although having strong presumptive evidence, had not been proved to be true erythroblastosis by the usual serologic tests.

In 1935 Pasachoff[11] reported the first case of the combined lesion. This was the case of M, a full-term Negro girl, the first child of healthy parents. The child was jaundiced with moderate hepatosplenomegaly, erythroblastosis (40 erythroblasts per 100 white blood cells), with abnormal shape and staining of the red blood cells but no anemia. There were some green meconium stools, but they became acholic on the

TABLE I. SUMMARY OF

AUTHOR	JAUNDICE	ANEMIA	ERYTHRO-BLASTOSIS	RH	RH ANTI-BODIES (MOTHER)	BILE IN URINE
1. Pasachoff 1935	1st day	5,350,000	40/100 wbc's	Not tested	Not tested	
2. Sanford 1940	Icterus 500 Bilirubin 35 mg.	1,600,000	162,000/ cu.mm.	Not tested	Not tested	
3. Skelton and Tovey No. 1 1942	1st day	Not reported	Not reported. See autopsy	Father pos. Mother neg.	Not tested	Present
4. Skelton and Tovey No. 2 1940	1st day	Not reported	Not reported	Father pos. Mother neg. Baby pos.	Not tested	Present
5. Lightwood and Bodian 1946	3rd to 11th day 7th week	1,500,000	2/100 wbc's	Mother neg. Baby pos.	None at 9 weeks	Present
6. McGeehan, Butchart, and Walker 1951	1st day	2,420,000	110/100 wbc's	Father pos. Mother neg. Baby pos.	1:8,000	Present

fourth day. The jaundice increased but there was no note of the level of the serum bilirubin. The patient died on the fifth day after developing neurological manifestations. Post-mortem examination showed:

1. Extramedullary hematopoiesis.
2. Kernicterus.
3. Complete atresia of the cystic, hepatic, and common bile ducts and no ampulla of Vater.
4. Cerebral aplasia.

This case was reported in the days before Rh testing and so these determinations were not made.

In 1940 Sanford[13] mentioned a case of a newborn infant with complete atresia of the bile ducts who had an anemia of 1,600,000 red blood cells, erythroblastosis (162,000 erythroblasts per cubic millimeter), and jaundice (35 mg. bilirubin per 100 c.c. of blood). There was, however, no mention of Rh determinations having been made.

In 1945 Skelton and Tovey[14] reported two cases of erythroblastosis associated with congenital atresia of the bile ducts.

Case 1 was the second child of an Rh-positive father and Rh-negative mother. The child's Rh was not tested and anti-Rh agglutinins were not demonstrated in the mother's blood three years after the baby's birth. The child

CASES REPORTED TO DATE

ACHOLIC STOOLS	LIVER	SPLEEN	OPERATION	DIED	AUTOPSY	COMMENT
4th day	Enlarged	Enlarged	None	5th day	1. Extra medullary erythropoiesis 2. Kernicterus 3. Congen. atresia of bile ducts 4. Cerebral aplasia	Not shown to be erythroblastosis.
			None		Atresia of bile ducts	Not shown to be erythroblastosis. Erythroblasts extremely high.
				2nd day	1. Erythroblastosis 2. Extramedullary erythropoiesis 3. Fibrous obliteration of common duct 4. Kernicterus	Presumed to be erythroblastosis from autopsy findings.
Present			Cholecystogastrostomy Fibrous occlusion common duct	Recovered	None	Presumed to be erythroblastosis from Rh determinations but suggestive from family history. Congen. atresia not proved.
Present			Atresia of bile ducts inoperable		1. Cirrhosis of liver 2. Atresia of cystic, common, hepatic, G. B. 3. Enlarged spleen 4. No extramedullary erythropoiesis	Not shown to be erythroblastosis.
Present	Enlarged	Enlarged	Atresia of bile ducts. Inoperable	100th day	None	

was jaundiced on the first day, had bile in the urine, and died on the second day. Necropsy findings were:

1. Erythroblastosis.
2. Extramedullary erythropoiesis.
3. Fibrous obliteration of the common duct.
4. Kernicterus.

Case 2 was the second child of an Rh-positive father and Rh-negative mother. The child was Rh positive and the mother's blood was not tested for anti-Rh agglutinins although two subsequent pregnancies resulted in the death of the newborn-jaundiced infants. Rh antibodies were demonstrated in the mother's blood in these later pregnancies. This child developed jaundice on the first day of life, and had bile in the urine and clay-colored stools. Cholecystogastrostomy was performed for fibrous occlusion of the common duct and the child recovered.

The same authors mention a third case, a child of an Rh-positive father and Rh-negative mother who developed jaundice and died on the tenth day of life. The autopsy showed congenital obliteration of the common bile duct.

In 1946 Lightwood and Bodian[7] reported a case of a newborn infant who had jaundice in the first two weeks of life which cleared up but recurred at the age of 7 weeks. The child was

anemic (1,500,000 red blood cells per cubic millimeter) but had only 2 erythroblasts per 100 white blood cells. The urine contained bile and the stools were acholic. The baby was Rh positive and the mother negative but she was not shown to have anti-Rh agglutinins in her blood. The child was operated upon at the age of 4 months for persistent jaundice. Complete atresia of the bile ducts was found as well as cirrhosis of the liver. Autopsy showed:

1. Cirrhosis of the liver.
2. Splenic enlargement.
3. Congenital atresia of the cystic and common ducts and a very narrow hepatic duct.

No extramedullary hematopoiesis was noted.

On admission to the hospital, her physical examination revealed nothing abnormal except that her uterus was enlarged to the size of a seven months' pregnancy, and she had grade 2 pitting edema of the extremities. Her blood pressure was 132/80 and remained below 130 during her hospital stay. Her urine contained a trace of albumin during this time. Her blood count was not abnormal. The toxemia responded well to treatment. On the third hospital day, November 7, her saline agglutinins were 1:64 and albumin antibodies 1:4,000. It was decided that induction was not indicated because of prematurity. However, on November 13, the saline agglutinins were 1:128 and albumin antibodies 1:8,000, and induction of labor was decided upon because of the rapidly rising antibody titer; but on the night of November 14, spontaneous labor began and a 6-pound, 2 ounce male baby was born after approximately a one-hour labor. The delivery was uneventful. The vernix caseosa was yellow and the amniotic fluid was brown stained. The placenta was normal. The mother's post-partum course was uneventful.

TABLE II. RISING ANTIBODY TITER DURING THE SEVENTH MONTH OF PREGNANCY

DATE	SALINE AGGLUTININS	ALBUMIN ANTIBODIES	COOMBS TEST
9-14-50	1:32	1:32	Positive
10-14-50	1:32	1:256	
10-17-50	1:32	1:1,000	
10-31-50	1:32	1:1,000	Positive
11- 7-50	1:64	1:4,000	
11-13-50	1:128	1:8,000	

CASE REPORT

Mrs. J. B., a 33-year-old white woman, was admitted to Saint Luke's Hospital on Nov. 4, 1950, for mild toxemia of pregnancy, complaining of excessive weight gain, ankle edema, and spots before her eyes. She was seven months pregnant and the expected date of confinement was Jan. 2, 1951. She had one previous pregnancy seven years before and that one child was living and well. She was Rh negative and the serology was negative. On Sept. 14, 1950, the anti-Rh saline agglutinins and the albumin antibodies were positive in a dilution of 1:32 and the indirect Coombs test was positive. On October 14 the albumin antibodies were increased to 1:256 and on October 17 to 1:1000 (Table II).

The baby was Rh positive, weighed 6 pounds, 2 ounces, and was normal in all respects. Jaundice was noted in the first hour by the nurse. The skin was dusky but the sclerae were greenish yellow. The blood count taken at birth was 11 Gm. of hemoglobin, 2,420,000 red blood cells, 67,000 white blood cells, and rubricytes 110 per 100 white blood cells. The direct Coombs test was positive. Two blood transfusions were given the following day and two on the day after. On the third day of life, the blood count was 19 Gm. of

hemoglobin, and 5,960,000 red blood cells. Thereafter, the blood count remained stable at a somewhat lower level and required only occasional transfusions (Fig. 1). The patient was listless and irritable from the fifth day of life. On the thirteenth day of life surgical consultation was requested because of the persistent jaundice, dark urine, and clay-colored stools from the seventh day of life. The serum bilirubin was 20 mg. per cent, icterus index 170, and the urine contained bile but no urobilinogen. The decision was

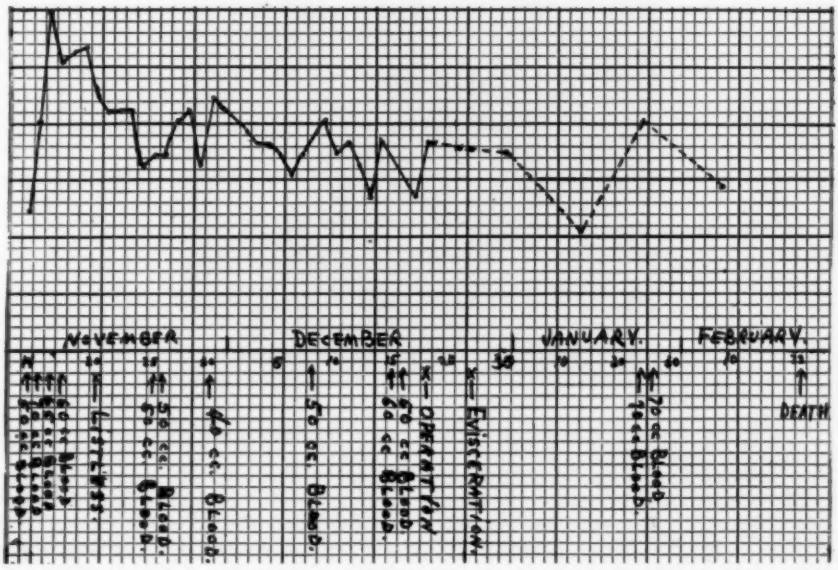

Fig. 1.—Clinical course.

made to delay surgery and watch the progress of the patient. After four more weeks of observation, the patient did not improve. His weight did not increase and his blood count fell to 3,700,000. The jaundice diminished somewhat to an icterus index of 110, the stools were still acholic, and the urine contaned bile and no urobilinogen.

On the thirty-fourth day, operation was performed (Fig. 2). A right rectus incision was made and the gall bladder region was exposed. The liver was quite large but otherwise appeared normal. A small, rudimentary gall bladder was seen; the cystic duct led from the gall bladder downward toward the hepatoduodenal ligament which was examined thoroughly, but nothing in the way of a bile-filled duct could be found. The gall bladder was opened and it contained only a drop or two of brownish mucus. The lumen of the cystic duct was obliterated as a fibrous cord and a probe or ureteral catheter could not be passed downward toward the area of the common duct. The entire area from the porta of the liver to the duodenum was carefully dissected and no evidence of a common or hepatic duct was seen. The dissection was carried about 2 cm. into the liver substance at the porta hepatis and no evidence of a bile-filled duct was found. The hepatoduodenal ligament was dissected carefully and no bile-filled duct or fibrous cord as a remnant of the common or hepatic duct could be seen although the portal vein was

easily visualized. The left lobe of the liver was then mobilized with the intention of resecting the left lobe to anastomose an intrahepatic duct to an available segment of gut after the method of Longmire[8]; but after some consideration, this was abandoned and no attempt was made to find the bile duct in the left lobe because the condition of the patient was not good and extensive surgery was considered unwise. The abdomen was closed without further surgery.

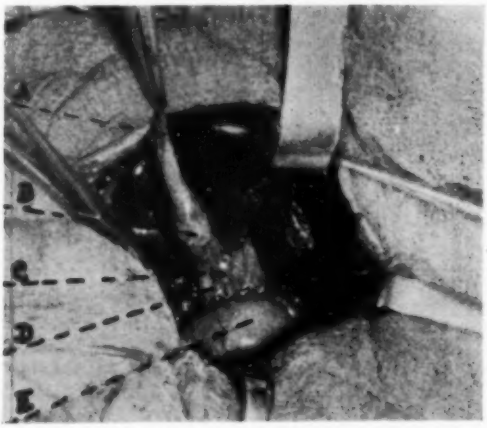

Fig. 2.—Showing the rudimentary gall bladder leading to the fibrous cystic duct. The hepatoduodenal ligament is dissected up to the porta hepatis and no evidence of a hepatic or common duct was found. *A*, Liver; *B*, gall bladder; *C*, cystic duct; *D*, hepatoduodenal ligament; *E*, duodenum.

The immediate postoperative phase was uneventful. The child had received 30 c.c. of blood during operation and the red blood cell count the next day was 3,600,000. The fluid and electrolyte balance was maintained and on the second postoperative day formula by mouth was begun. On the fourth day, the patient developed paralytic ileus with marked distention, and on the sixth day he developed dehiscence of the wound and evisceration. Secondary repair was immediately performed with the use of through-and-through wire sutures. Postoperatively, severe paralytic ileus recurred. The wound did not do well; healing was very poor, and a large ventral hernia developed. At this time, the patient was eating poorly and losing weight; it looked as though he would not survive. He developed opisthotonus on the tenth postoperative day. However, from this date onward, the patient's condition remained unchanged. The abdomen healed and he gained some weight but then remained between 6 and 6½ pounds. During this time, jaundice and opisthotonus continued although the icterus index fell from 170 to 41. The abdominal distention receded. The bowel movements became normal except for color; they remained clay colored until the thirtieth day of life and then remained light yellow until death. (The yellow color was presumed to be due to the small amount of bile in the feces by way of the intestinal mucosa.)

The patient was discharged on Feb. 18, 1951, the ninety-sixth day of life. His weight was up to birth weight, he was taking formula well, the bowels were moving, yellow in color. The abdomen was healed by granulation, the child was in opisthotonus position and had deep dusky jaundice with greenish discoloration of the sclerae. The patient died at home on the hundredth day of life after two hours of coma. Autopsy was refused.

COMMENT

The concomitant occurrence of congenital atresia of the bile ducts and erythroblastosis fetalis is uncommon; when they do occur together, they produce symptoms of both conditions merged one with the other. Their occurrence together and in different members of the same family is highly suggestive, but we cannot agree with the opinion expressed by some authors and it would seem illogical to assume from the evidence at hand that an etiological relationship exists between the two.

In five cases reported in the literature and one additional case which we have observed and which is reported in detail here, we find no evidence in this small number of cases to support the view that bile plugs cause fibrosis and organization in the intra- and extrahepatic bile ducts. Furthermore, it seems highly unlikely since bile plugs could not have time to occur and fibrose and organize in the short space of time of the last few days of intrauterine life. If, indeed, there are any pathologic changes occurring during intrauterine life in the biliary passageways in erythroblastosis fetalis, it would seem to us incredible that a completely foreign substance like a bile plug could or would organize. We know of no evidence to support the suggestion that Rh antigen-antibody reactions can produce these effects in the ducts. The antibodies of erythroblastosis are apparently not produced before the fifth month of intrauterine life, which is long after the biliary tract is well developed and functioning. It would seem impossible, therefore, that antigen-antibody reaction at this time could produce any effects in the well-developed ducts. None of these explanations adequately explain the aplasia of the gall bladder and cystic duct found in our case.

We tend to favor the theory that these are two independent conditions existing simultaneously and that the pathogenesis in these cases is similar to simple congenital atresia and probably due to the failure of the normal establishment of a lumen and an arrest at the solid stage of embryonic development of the extrahepatic bile ducts. This stage of development is complete by seven to twelve weeks, which is long before the appearance of Rh antibodies that may affect the child, which begin to appear in the fifth intrauterine month. It is highly unlikely, therefore, that hepatic cell damage by antigen-antibody reaction or duct change by bile thrombi can produce the absolute absence of extrahepatic bile ducts as seen in these children.

The therapy of congenital biliary tract atresia has been discussed by previous authors and, as has been emphasized by Ladd and Gross, operation should be performed as soon as diagnosis is assured. It must be borne in mind, however, that occasional cases of erythroblastosis may develop a transient obstructive phase due to intrahepatic biliary obstruction that may last for a period of a few weeks to a few months and in which operation is contraindicated. Exploration should be delayed for a few months and erythroblastosis should be treated with blood transfusions until the child's condition is optimal for major surgery and until the diagnosis of extrahepatic biliary obstruction can be fairly definitely assured. Exploration may reveal a normal biliary tract which is obstructed by a bile plug or actual atresia of one or all of the extrahepatic ducts. The latter condition may be corrected only

if there is an available bile-filled duct to anastomose to an adjacent portion of gut. This situation, and therefore operability, is present in only a small percentage of cases estimated at about 20 per cent. Since in the remaining 80 per cent the outlook is universally fatal, it occurred to us to consider the possibility of performing the Longmire procedure in the hope that an intrahepatic duct might be found to utilize in anastomosis. In spite of the disappointing experience of Longmire in three patients with congenital biliary atresia,[9, 10] this procedure should be considered if possible. It was not performed in our case because of the child's general condition, but it is hoped that in the future this may be feasible in a desperate attempt to save an otherwise hopeless case.

SUMMARY

1. The etiology of congenital atresia of the bile ducts occurring in erythroblastotic children is discussed.

2. The differential diagnosis is described.

3. A review of the five cases reported in the literature is given.

4. An additional case is described in detail.

5. Therapy is discussed.

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GROWTH AND DEVELOPMENT OF INFANTS RECEIVING A PROPRIETARY PREPARATION OF EVAPORATED MILK WITH DEXTRI-MALTOSE AND VITAMIN D

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SINCE early attempts by Liebig, Biedert, and others, starting a century ago, to find an adequate substitute for human milk, the number and variety of formulas devised for infant feeding have been legion. Although any lengthy review of the history along these lines has no place in the present discussion, it is of interest to recall the eras in this development as outlined by Anderson.[1] The first, or "scientific," era, starting in the latter half of the nineteenth century with its detailed analyses and endeavors to reproduce human milk as exactly as possible, persisted over a fairly long period. In the more recent past, the "psychologic" era reached its climax in demand feeding. The present era is characterized by a tendency toward "streamlining the infant feeding." Brennemann comments, "There was for a long time an ever-increasing complexity of ideas, theories, and practices that from without seemed, and often was, chaotic . . . To-day we have emerged from this chaos of complexity into what one might call a chaos of simplicity. We no longer evolve formulas with the help of algebraic equations; we are actually confronted in a given case by the question of which simple method of feeding to choose."[2]

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In view of the study here reported, this is a most pertinent statement. Nor would it seem that this tendency toward simplification is an undesirable one—not because the present-day mother is lazy, but because there is little gained from hours spent over formula preparation. Freed from this, the young mother has more time to spend with her baby and with other children in the home. Then, too, the human factor of error which is introduced in formula preparation is related not only to the intelligence of the mother, but to the number of procedures involved with the consequent risk of miscalculations, wrong measuring, and contamination. Therefore, in so far as simplification is compatible with equal nutritional value, it is an admirable motive. It was in an attempt to evaluate such a simplified preparation that the present study was undertaken.

Evaporated milk fortified with Vitamin D long has been one of the most popular and widely used foods for artificial feeding. Its advantages are well known and need no reiteration here. When carbohydrate is added to increase calorie value, and when properly diluted and supplemented with vitamins, it adequately meets the needs of the normal young infant.

With the object of supplying in one container two generally accepted

foods, evaporated milk with 400 units of vitamin D, and Dextri-Maltose, making possible the preparation of a formula merely by the addition of warm water, a product has recently been made available for preliminary study.* Carbohydrate has been added to the milk under study to give a total of 17.1 per cent in the undiluted, or 8.5 per cent in standard dilution of 1:1. The protein content is comparable to that of cow's milk in the dilution usually used in the first six to seven months, which is the period during which a formula such as that under consideration is most useful. (See Table I.)

Table I. Comparative Analyses of Different Kinds of Milk*

	PROTEIN %	CARBOHYDRATE %	FAT %	CALORIES/OUNCE
Human milk*	1.5	7.3	3.5	20
Cow's milk*	3.5	4.9	3.9	20
dilution 4:1	2.8	3.9	3.1	16
Evaporated milk*	7.0	9.9	8.0	44
dilution 13:19	2.8	3.9	3.2	17
Similac 1:8†	1.5	6.8	3.4	18.9
SMA 1:8†	1.3	7.3	3.5	20
Biolac 1:1.5†	2.8	7.4	2.8	20
Lactum	5.3	17.1‡	10.2	40
dilution 1:1	2.6	8.5	5.1	20

*Values taken from Jeans and Marriott: *Infant Nutrition.*
†Values taken from Mitchell-Nelson: *Textbook of Pediatrics.*
‡Milk content, 7.0 per cent.
Dextri-Maltose, 10.1 per cent.

During the period of this study, fifty-seven infants from the Well-Baby Clinic of the Department of Pediatrics received this preparation, twenty-eight male infants, twenty-nine female. These were normal infants whose parents for the most part were graduate students at the University, and could be depended upon for accurate observation and reports. The period of observation ranged from two months in one case to ten months in one case, covering 354 total infant months, an average of 6.1 months per infant.

Although several premature infants were given Lactum at a relatively early age with good results, their records were not included in the present tabulations. Early in the study it was decided to begin the feeding of this preparation when the infants weighed approximately 10 pounds, as the smaller infants are more likely to need adjustments of formula to meet their individual needs. However, as the study proceeded, this limit was lowered. Ten weighed less than 10 pounds when the new regimen was started, the smallest weighing 7 pounds, 11 ounces. The youngest was a 3-week-old infant; 25 per cent were under 7 weeks of age when they began taking this formula.

The infants were examined at approximately monthly intervals to evaluate their growth and development. At each examination, data were obtained regarding degree of tolerance to the milk as shown especially by amount of regurgitation and normaley of bowel pattern, physical growth as reflected in length and weight increments, bone development as measured

*Lactum, Mead Johnson and Company.

by ossification of carpal bones, motor development, incidence of infection, and the hematological picture as reflected by hemoglobin and red blood cell values.

Early in the study, dilutions higher than 1:1 were attempted in the younger infants. However, this was found in a number of cases not to satisfy hunger. The 1:1 dilution was thereafter advised in most cases. All received vitamin supplement in some form, either a multiple vitamin preparation,* or cod liver oil and orange juice. The water-soluble preparation was given early, one-half teaspoonful daily, in order to supply 25 mg. of vitamin C, the total vitamin D thus being about 900 units, which is more than the daily requirement but below the toxic level. Later orange juice was substituted in order to supply vitamin C from a natural source, and small amounts of cod liver oil were given to introduce it to the infant and thus prepare him for the regular daily dose when the present formula was stopped. From the age of 2½ to 3 months additional foods were given, usually starting with egg yolk, then adding strained vegetables, fruits, and meats. As is observed in any group, the readiness with which solids were accepted varied. Of course, once this regimen has become established, nutritional status is a result not only of the formula but of the whole dietary picture.

One of the main points of interest in this study was the effect, if any, of the constant carbohydrate content on the number and consistency of the stools, since it has been rather generally assumed that these are directly related to the amount of carbohydrate in the formula. Jeans states that "Any sugar when fed in excessive amounts may cause gastrointestinal fermentation and diarrhea. The sugars which have smaller molecules, such as the monosaccharides . . . and disaccharides . . . when in solution have greater osmotic pressures than the higher carbohydrates such as dextrin and starch. Solutions of dextrose stronger than six per cent, or of milk and cane sugar stronger than eight per cent, are hypertonic and likely to exert some laxative effect for that reason alone, aside from fermentation."[3] Combinations of dextrin and maltose, early and late breakdown products of starch hydrolysis, have been widely and satisfactorily used. Dextrin is not readily fermented in the gastrointestinal tract, a desirable quality in a sugar for use in infant feeding. And, according to Jeans, its conversion into maltose occurs at a speed not much more rapid than that of maltose to dextrose so that it is not permitted to remain long in the intestines of normal infants and thereby encourage fermentation.

Stools were considered normal if they were soft and partially or wholly formed, and not more than four a day. Changes believed due to the presence of infection were not considered significant. Of course, in some cases, the picture was not a constant one, varying no doubt with the quality of other foods eaten. In no case was there any history of persistent diarrhea. In forty-eight infants, the usual number of stools was one to two daily; in only nine were there three, or occasionally four a day. In three young infants,

*Polyvitamin Dispersion, Mead Johnson and Company.

five or more stools a day were reported early with no apparent cause, but this cleared spontaneously in each case.

Regurgitation is a fairly common complaint for young infants in any group. The actual relationship of this to the content of the formula may often be questioned due to the possible influence of other factors, such as emotional instability in the mother or both parents, attempts to make the infant take a specified amount at each feeding, and the mechanics of feeding, as position, ease of burping, and nipple hole size. In six infants in this group, regurgitation occurred to more than a mild degree over a period of several months. In only one case, however, was another formula given in an attempt at its correction. In two other infants there were brief complaints of spitting up which, however, did not persist. This number is not out of proportion to those found in any group of infants on varied feeding regimens.

Records of height, head circumference, and weight for given ages were plotted on the growth charts used routinely in the Department of Pediatrics.[4, 5] It was found that the mean values for length for both boys and girls follow a curve parallel to and somewhat above the average of the Iowa growth standards (Table II and Fig. 1). Although the mean birth weight for both sexes approximated the general average for full-term infants, at 1 month of age both boys and girls tend to be above average weight of the growth chart. The curve of mean weight of the boys parallels the average at a higher level through eight

TABLE II. THE MEAN AND STANDARD DEVIATION VALUES OF HEIGHT AND WEIGHT ACCORDING TO AGE OF INFANT BOYS AND GIRLS RECEIVING LACTUM

	HEIGHT			WEIGHT		
	NUMBER	MEAN	STANDARD DEVIATION	NUMBER	MEAN	STANDARD DEVIATION
			Boys			
Birth	–	–	–	27	7.5	1.15
1 mo.	8	21.8	0.85	8	9.7	1.37
2 mo.	19	23.1	0.97	19	11.8	1.47
3 mo.	25	24.4	0.82	25	14.0	1.22
4 mo.	28	25.5	0.81	28	15.6	1.46
5 mo.	27	26.4	0.82	27	17.0	1.72
6 mo.	26	27.1	0.89	26	18.4	1.81
7 mo.	25	27.8	0.84	25	19.4	1.85
8 mo.	20	28.4	0.98	20	20.4	2.05
9 mo.	11	28.8	1.21	11	20.4	2.24
10 mo.	5	28.8	–	5	20.3	–
			Girls			
Birth	–	–	–	27	7.3	0.76
1 mo.	5	21.5	–	6	9.9	–
2 mo.	13	22.8	0.67	13	11.3	0.98
3 mo.	25	24.0	0.85	25	12.9	1.42
4 mo.	28	24.9	0.85	28	14.2	1.56
5 mo.	27	25.8	0.78	27	15.6	1.65
6 mo.	27	26.6	0.85	27	16.9	1.86
7 mo.	24	27.1	0.96	24	17.9	2.13
8 mo.	17	27.7	0.88	17	19.0	2.31
9 mo.	6	27.9	–	6	18.4	–

months. The mean weight of the girls is above that of the standard to the fourth month, from which time to the eighth month it coincides with the latter.

Each subject was classified as to body build both at the beginning and end of the period of observation. In length the infant was rated average, tall, or short, depending on the relationship between the infant's measurements and the standard curve. Weight type was then determined by relating weight to individual height. If it approximated the same relative level it was considered average for that infant. If it deviated widely above or below the expected level, the infant was considered respectively stocky or slender. The body length values for the individual infants when plotted on Iowa growth charts show that thirty-two, or 56 per cent, made average gains in length, twenty, or 35 per cent, made greater than average gains, and five, or 9 per cent, made less than average gains in length.

The weight values for the individual infants when plotted on the Iowa growth charts show that of the fifty-two patients who made average or greater gains in length, forty, or 70 per cent, of the total group made comparable gains in weight. Ten, or 18 per cent, made gains in weight less than expected for their age and height increments, and two, or 3 per cent, made more than expected weight gain for their age and height increment. Five, or 9 per cent, did not make average gains in either length or weight during the study period.

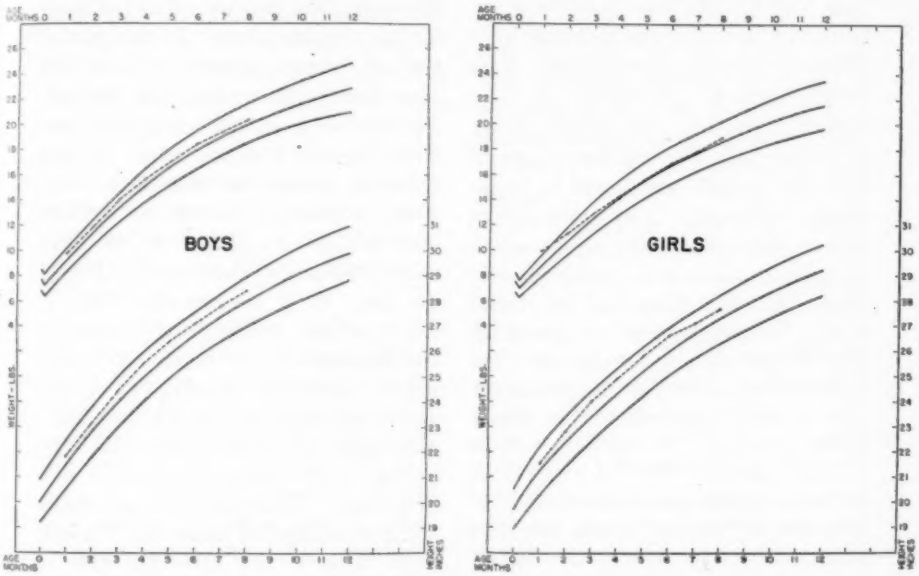

Fig. 1.—The curves of mean values of height and weight for infants receiving Lactum (------) are superimposed on Iowa growth standards. The infants were given Lactum at varying ages: 25 per cent were under 7 weeks of age when they began taking the formula. See Table II for the number receiving the formula at each month.

The unsatisfactory physical growth of the five infants could be explained by factors other than the type of feeding they were receiving. Further study of the five infants whose growth was unsatisfactory in length and weight revealed that in one infant there was a short period of deceleration definitely related to intercurrent infections associated with mild diarrhea, and in addition one of the infants had his usual routine upset by a death in the immediate family. Two infants failed to gain well before, during, or after they were receiving the special formula. The mother of one of these two infants was found to be insecure emotionally. The other infant received the formula for a four-month period and did as well on this formula as on others that were tried before and after. The development of the latter was delayed despite the fact she had normal blood values for calcium, phosphorus, and phosphatase. The fourth infant received the special formula for four months. She did well with it for two months, and then during the last two months her length fell from slightly above the average to slightly below while her weight fell from average to slightly below. The child's motor development was above average and she was a very active, well baby. The fifth infant received the special formula five months. Both height and weight fell gradually from average to low normal. The baby was happy and his motor development was normal.

In an attempt to evaluate maturity on the basis of bone growth, roentgenograms of the hand were taken of fifty infants, of whom eleven had two and three had three interval films. Of these, thirty-nine included films taken at the age of 6 months or more. Estimation of normal ossification in infancy was found to be difficult due to the arbitrary standards set at three-month intervals, in which the examiner is confronted with the problem of normal range for age.* Sontag and Reynolds,[6] recognizing the limitations of using the hand as the sole criterion, recommend using a number of centers. However, this does not seem practical for the average study. In this study, two of thirteen infants who showed some degree of retardation on the first film showed a similar picture on one later interval film, and three on two follow-up films. Of these five, four were 9 months or older when the last one was taken. Three of the five showed normal or above normal height for age. It is recommended that in any further similar study periodic roentgenograms be taken at three-month intervals, starting at birth, since, especially during the first year, estimation of progress is more important than a single estimate at any given age. "Important as it is to know the general level of maturity, it is still more important to know the rate at which maturity is progressing."[7]

Motor development was recorded with the use of the Aldrich and Norval development graph.[8] Of the total number, two showed distinctly accelerated development, two were retarded. Motor development is to be considered a function not only of nutrition and of mental endowment, but also of degree of stimulation in the environment. As was previously mentioned, the parents in this study were for the most part

*Evaluation of bone age was made by Dr. Eugene Van Epps of the Department of Radiology, University Hospitals, Iowa City, Iowa.

graduate students in the University, and there is little doubt that the infants were, in most cases, given more than the usual motivation to performance.

Adequate nutrition at any age is generally believed to be an important factor in the prevention of infection, others being the home environment and the number of persons in the household. Of the group studied, in twenty-two, or 38.6 per cent, no upper respiratory infections were recorded during this period. In eighteen, one was recorded, in nine, two were recorded, and in eight, three or more. Of the sixty-five infections recorded, forty-three were mild and seventeen were moderate to severe. Antibacterial therapy was used for the more severe infections.

In view of the light thrown on the nutritional origin of megaloblastic anemia in infants in the past few years, observations along this line are important when evaluating any feeding regimen. May and associates have recently concluded from their studies on monkeys, in which they produced an anemia simulating that in infants, that it is related not to the milk as the sole factor but to the absence of vitamin C.[9] It was previously stated that all the infants included here received adequate vitamins. There was no clinical evidence of anemia. Hemoglobin values averaged consistently throughout the whole group from 11.3 to 12.0 grams, with red blood cells 3,800,000 in those under 3 months of age, to 4,380,000 in those over 7 months. Twenty-seven of those aged 3 months and over received 7.5 mg. of iron in form of ferrous sulfate* daily, as Stearns has demonstrated at this age the stored iron begins to be depleted, and it is desirable to protect this supply until diet is adequate in iron-containing foods.[10]

A very practical aspect, the ease of preparation of this formula, should not be overlooked. With a small opening in the can, it can be kept in the refrigerator during the day, each bottle being prepared as needed simply by pouring the desired amount of milk into the clean, not necessarily sterilized, bottle, and adding hot boiled or tap water to give the desired dilution. Nipples should be sterilized as usual. In this way, it is also easy to adjust the amount prepared to the appetite. If too little has been made, it is a simple matter to prepare more. There is consequently less temptation to push the infant to take more than he desires. Mothers have been consistently pleased with this formula, particularly from the standpoint of the ease with which it may be prepared.

*Fer-In-Sol, Mead Johnson and Company.

SUMMARY

Fifty-seven young infants have been observed over a varying period up to 10 months of age while receiving a simplified formula consisting of evaporated milk fortified with 400 units of vitamin D and Dextri-Maltose to which water alone is added in preparation. On the basis of this study, it has been shown that infants fed this formula (with vitamin supplements and the usual additions of solid foods) have mean height and weight curves slightly above normal, and a normal or superior picture of general development. These facts, with the ease of preparation, combine to make it a most useful addition to the field of infant feeding.

The authors acknowledge the help of Mrs. H. G. Kelly in the statistical work involved in this study.

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ELECTROCARDIOGRAPHIC CHANGES IN EXCHANGE TRANSFUSIONS

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IN JANUARY, 1951, Furman and his associates[1] reported studies on electrocardiographic changes occurring in replacement transfusions. In their technique 1 Gm. of calcium was added at the conclusion of each transfusion. They were able to demonstrate electrocardiographic changes in all six of their patients due to changes in the calcium level. These changes involved the Q-T interval, the height of the T wave, and the rate.

At Raymond Blank Memorial Hospital electrocardiograms were taken during exchange transfusions to determine (1) whether frequent injections of calcium were necessary; and (2) to attempt to judge the effect on the heart when the procedure was finished in an unusually short period of time.

METHODS AND MATERIALS

Eight patients with the diagnosis of erythroblastosis were studied. The ages of the babies at the time of starting the replacement transfusions varied from 2 to 38 hours. They weighed between 2,380 and 4,330 grams. All received 500 or 520 c.c. of citrated, type O, Rh-negative blood. The time required for the exchanges varied from 50 to 110 minutes with an average time of about 75 minutes. All except one of the babies had initial red blood counts under four million. The Coombs test was positive in all cases.

From the Raymond Blank Memorial Hospital for Children.

The exchange transfusions were all carried out through the umbilical vein using the 20 c.c. out-20 c.c. in method. Venous pressures were determined as recommended by Diamond and his associates.[2] Two-tenths calcium gluconate was injected into the umbilical vein after every 100 c.c. of blood injected or when indicated by the electrocardiogram.

Electrocardiograms employing three standard and three unipolar limb leads were taken before starting and at the conclusion of each exchange. In addition a cathode ray electrocardiograph was run continuously during the exchange with frequent records taken before and at various intervals following the administration of calcium. Samples of the withdrawn blood were analyzed for serum calcium in three cases.

RESULTS

It was possible to demonstrate repeatedly that gross skeletal muscle tremors appeared after each 100 to 150 c.c. of blood were exchanged. These disappeared promptly after an injection of 2 c.c. of 10 per cent calcium gluconate. In the less sick babies this was clinically evident by fussing and crying. In the more severely ill babies the clinical evidence was lacking but the electrocardiogram revealed both this need and the immediate improvement following the administration of calcium. The tracings shown in Fig. 1 were taken before and after the administration of calcium.

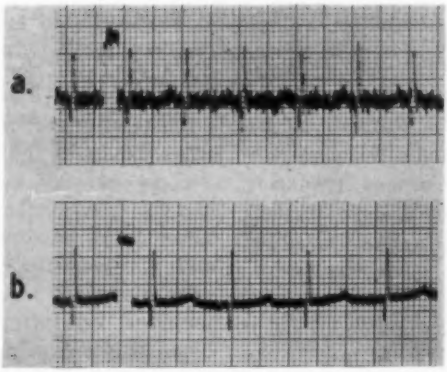

Fig. 1.—*a*, Tracing taken just before and *b*, just after the injection of 2 c.c. of 10 per cent calcium gluconate. In *b* the rate has slowed and the skeletal muscle tremors have disappeared.

Fig. 2.—Calcium determinations in relation to the injections of calcium gluconate.

A second effect of calcium administration was to slow the heart rate. In six of the eight patients the pulse varied from 90 to 150 beats per minute. After each injection of calcium the heart rate would slow rapidly and then gradually rise while the next 100 c.c. were being exchanged.

In most cases the Q-T intervals could not be accurately measured either because of the skeletal tremors or because the T wave was isoelectric. When it could be measured, no significant prolongation could be found.

The serum calcium levels of the withdrawn blood before and after the calcium injections were determined on three patients. The values in relation to the calcium injections are shown in Fig. 2. The high concentrations found in the first samples following the injection of calcium are probably due to contamination in the stopcock or catheter. Separate syringes were used and after the calcium injection 20 c.c. of blood were injected before the sample was drawn.

The electrocardiographic evidence of muscle tremors as well as clinical signs of irritability occurred with serum calcium values over 11 mg. per 100 c.c. The average calcium level of the citrated blood used for the exchanges was 7.6 mg. per 100 c.c.

Neither the injection nor the withdrawal of blood produced any constant changes in the heart rate. Furthermore the injection of 20 c.c. of blood in twenty to thirty seconds produced no more change in the electrocardiogram than slower injection. However, the babies cried and fussed more with the rapid injection and at these times the rate occasionally would jump to between 160 and 180.

Contrary to expectations, electrocardiograms taken ten minutes after finishing the exchanges showed no significant differences from the initial tracings regardless of the length of time required for the procedures. In none of the eight was the heart rate more than ten beats per minute different in the initial and final tracings. There was no change of axis. In two patients the T waves were slightly more prominent at the conclusion of the procedures.

DISCUSSION

Although our procedure was somewhat different from that of Furman and his associates,[1] our results were similar. Skeletal muscle tremors were frequent and were abolished by the administration of calcium. In some cases we exchanged up to 140 or 160 c.c. without giving calcium while waiting for either clinical or electrocardiographic evidence of calcium need. The electrocardiographic changes are dependent on ionized calcium and our determinations included that calcium bound to the citrate as well as that bound to the protein. Although we could not prove hypocalcemia by chemical determinations, the repeated effect of calcium injection leaves little room for doubt that a lack of ionized calcium existed. We feel that the injection of 2 c.c. of 10 per cent calcium gluconate after every 100 c.c. of blood is to be recommended.

The injection of 20 c.c. of blood in a newborn baby is the equivalent of 300 to 400 c.c. in an adult. As 20 c.c. was sometimes injected in twenty to twenty-five seconds, we had expected to find signs of dilatation of the right side of the heart. However, the elec-

trocardiograms showed no such effects. Even when the whole procedure was completed in one hour or less with repeated rapid injections, the electrocardiogram remained unchanged. Because the babies were more irritable when the exchange was hurried, we feel that an hour to an hour and a half should be used with each 20 c.c. of blood injected over a two-minute period.

SUMMARY

Eight babies with erythroblastosis were studied by continuous observation of their electrocardiograms while they were having replacement transfusions. Skeletal muscle tremors appeared after about each 100 c.c. of blood were exchanged and were abolished by the injection of calcium. There were no significant changes between tracings taken before starting and at the conclusion of the procedure.

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HYPOTHYROIDISM FOLLOWING THYROIDECTOMY FOR CONGENITAL OBSTRUCTIVE GOITER

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THE first report of congenital goiter was written by Fodéré in 1792.[3] Since that time many cases have been described in the European and Scandinavian literature.[14] In contrast to this, very few instances have been recorded in American publications.[2, 6, 9, 13, 15, 17] The first case of congenital goiter in Ohio or Minnesota, where the incidence of simple goiter is high, was not reported until 1939. In all the cases so far reported in the United States the mother showed some evidence of thyroid dysfunction, and in most of the cases had been treated with or received one of the iodine compounds as expectorants either before or during pregnancy. One report failed to indicate whether the mother did or did not receive iodine.[6] In the case to be described, the mother at no time received any of the iodine compounds. The child was born with an obstructive goiter which was removed surgically. Symptoms of hypothyroid function followed operation, and these were rectified by replacement therapy.

CASE REPORT

On Nov. 4, 1948, B. V., a 5-week-old male infant, was admitted to The Mount Sinai Hospital. The patient was the result of the third pregnancy; the two siblings were normal children, 16 and 4 years of age. This child was born at home after a full-term pregnancy and normal delivery. At birth, three lumps were noted in the infant's neck. The birth weight was unknown. During the first week the infant experienced difficulty in swallowing, with several choking episodes. Peculiar gurgling sounds in the throat were heard. During the ensuing four-week period the sounds had increased in severity and had been associated with tachypnea. The size of the cervical masses had not been observed to have increased materially. The infant had never become cyanotic, and it was noted that he preferred to lie with his head hyperextended.

The parents were both natives of New Jersey. There was no family history of any thyroid disturbance. The paternal grandparents were born in Holland and settled in the United States in 1890. Of possible significance is the observation that the mother had had several "nervous breakdowns" in the past, and at the time of the infant's admission was suffering from her most recent attack. She had never taken any thyroid medication or iodine-containing compounds.

On admission the child was a well-developed and well-nourished infant with a good cry, not hoarse, having no respiratory difficulty other than noisy respirations. The weight was 8 pounds, 9 ounces. The length was 21 inches. The head was maintained in hyperextension and could not be flexed without producing dyspnea. In the neck there were three masses. The submandibllar space and anterior triangles of the neck on either side were filled with soft, somewhat cystic, fairly well-demarcated masses. The mass on the right extended posteriorly beyond the angle of the jaw, and inferiorly into the base of the neck. The mass on the left was smaller and the inferior margin extended just to the base of the neck. The masses did not transilluminate, and both extended

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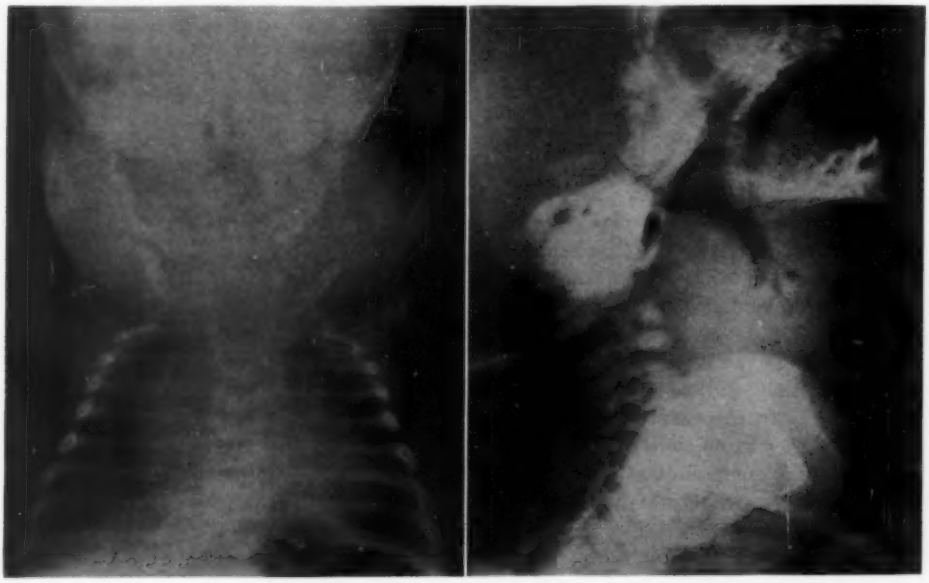
toward the midline where there was a third mass almost golf ball in size. No definite distinction could be made between the masses. In the midline, all the masses were below the level of the hyoid bone. The bridge of the nose was low. The cheeks were chubby and the eyelids were slightly puffy. The mouth was kept open, but there was no macroglossia and the tongue did not protrude. Digital palpation of the hypopharynx revealed a mass anteriorly by the masses described. No intrathoracic component was present. (Fig. 1, *A* and *B*.) The differential diagnosis on admission included cystic hygroma of the neck and multiple cysts of the thyroid.

On November 18, the patient was operated upon under intratracheal anesthesia by one of the authors (E. S. H.), with Dr. Ernest Arnheim. A curvilinear collar incision was made extending completely across the base



A. *B.*

Fig. 1.—*A*, Preoperative roentgenogram, anteroposterior projection. The rounded masses bulge from both sides of the neck. *B*, Preoperative roentgenogram, lateral projection. The head is hyperextended, and the hypopharynx markedly displaced anteriorly.

in the retropharyngeal area which was pushing the trachea and pharynx anteriorly. The other positive finding on admission was a grade 3 systolic murmur heard best at the base of the heart. No thrills were palpable and there was no precordial bulge. A small umbilical hernia was present.

The hemogram and the urine examination were normal. Roentgenograms of the neck revealed the esophagus and trachea to be displaced of the neck, with division of the platysma and strap muscles. It was apparent that the pathology was confined to the thyroid gland, which grossly had the appearance of a large goiter. All of the lobes were greatly enlarged, and the left lobe extended around and behind the larynx. The larynx was not completely encircled. The gland was uniformly firm in consistency and there was greatly increased vascularity. Because of considerable doubt as to the nature of

the underlying disease, a frozen section was performed on an excised portion of the gland. The tentative diagnosis was neoplasm of the thyroid and total thyroidectomy was advised. The left superior pole vessels were isolated, doubly ligated, and divided. The isthmus was mobilized and divided to the left of the midline. A total excision of the left lobe was performed with division of the middle and inferior vessels on the capsule of the gland. The right lobe was similarly mobilized and resected together with the isthmus, leaving only a small segment of thyroid tissue 1 cm. in diameter at the right inferior pole. At the right lower pole there was a firm marble-sized nodule which was removed together with the remainder of the lobe.

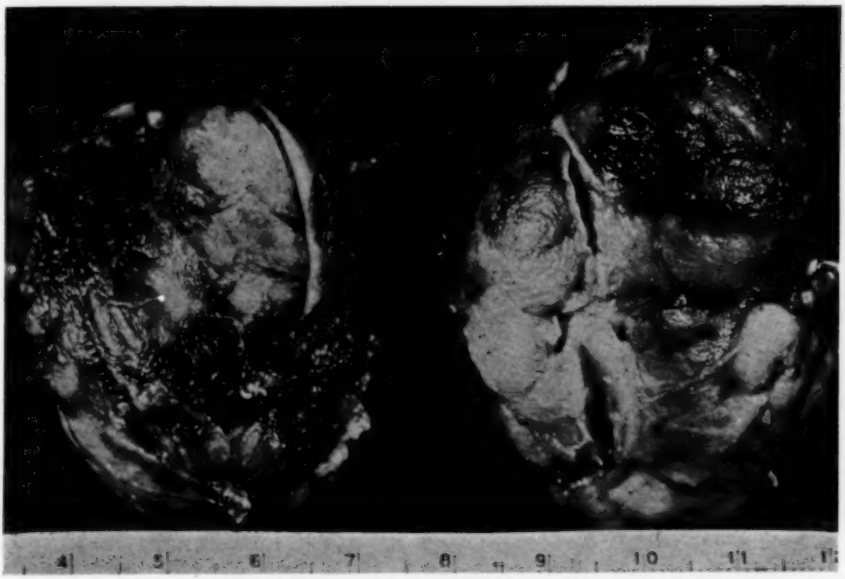
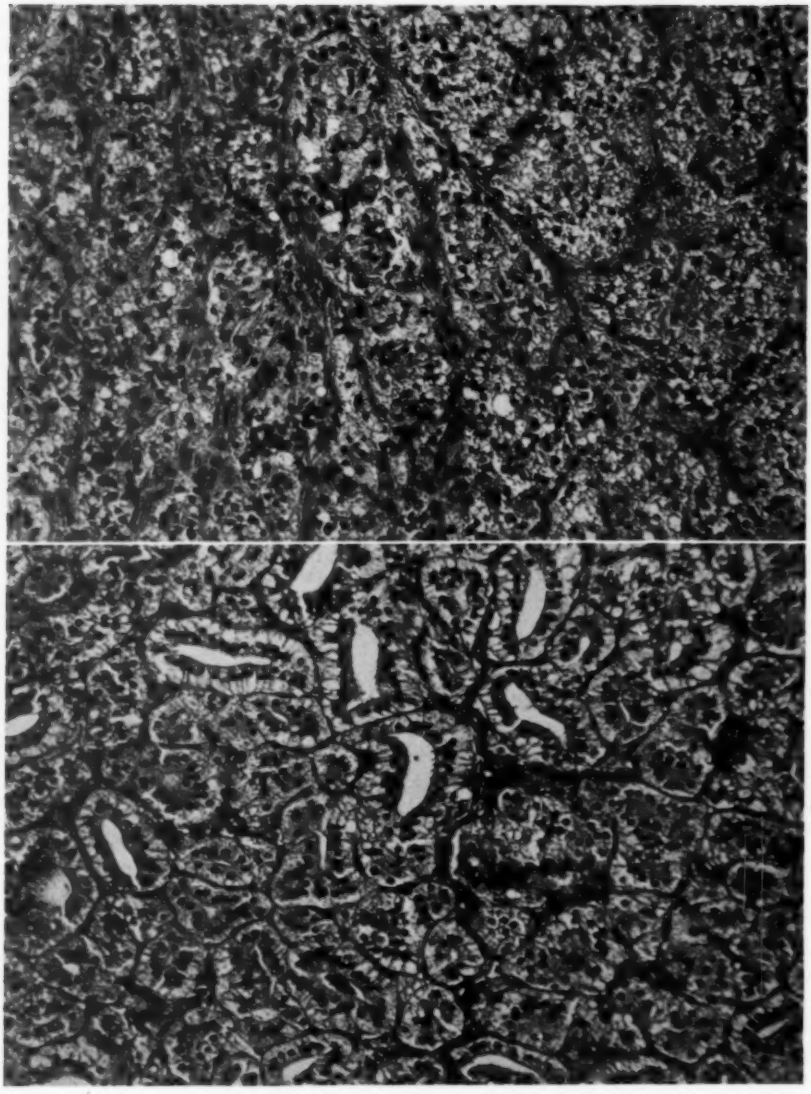


Fig. 2.—Anterior view of both resected lobes of the thyroid gland.

The gross description of the mass and the microscopic examination revealed the following: The specimen consisted of an elongated semilunar mass of thyroid tissue weighing a total of 65 grams. The mass measured 13 × 5 × 2.5-3.0 cm. (Fig. 2). The entire mass was enclosed in a thin fibrous transparent capsule. A dilated segment of vein coursed in a transverse direction along the anterior surface of the specimen. Upon opening the vein it was found to contain a moderate amount of clotted blood but appeared to be free of neoplastic invasion. Section of the mass revealed a soft, gray pink, cellular tissue irregularly arranged in variable-sized lobulations by very fine fibrous trabeculae. The microscopic report was thyroid showing changes compatible with a diagnosis of congenital diffuse parenchymatous stroma. (Fig. 3, *A* and *B*.)

The infant's postoperative course was uneventful except for moderate laryngeal edema which was secondary to the intubation anesthesia and the surgical manipulation in the laryngeal area. This was successfully treated by steam tent, frequent suctioning, and Adrenalin in the form of an aerosol. Tetany was not detected at any time.

A.



B.

Fig. 3.—Histologic structure of thyroid gland. Hematoxylin and eosin stain, ×185. *A*, The disorganized architecture in this area suggested a malignant lesion on frozen section. *B*, Typical acinar architecture, characteristic of most of the resected gland.

Laryngoscopy revealed normal motion of both vocal cords. The head could now be flexed normally, respiratory obstruction was eliminated, and there were no further episodes of choking during feeding. A roentgenogram no longer showed the tremendous anterior displacement of the trachea (Fig. 4).

Fig. 4.—Postoperative roentgenogram, lateral projection. The head can now be flexed, and much of the anterior displacement of the airway has been corrected.

In order to determine whether the patient had been receiving adequate thyroid hormone from the goitrous gland, roentgenograms were taken for bone age two days after operation. These revealed the presence of epiphyseal centers at the lower end of the femur and upper end of the tibia. The patient's bone age was therefore commensurate with his chronological age of eight weeks. Roentgenograms of the wrists failed to reveal the presence of carpal centers. The serum cholesterol value was 280 mg. per cent.

Dessicated thyroid was started on the seventh postoperative day as replacement therapy. Thyroid, U. S. P., ¼ grain, was given daily for eight days and then increased to ⅜ grain daily for nine days. At the end of the seventeen-day course of thyroid the drug was stopped. There was no change in the infant's appearance during the period of treatment. It was the intention of the pediatrics department, in stopping the drug, to give radioactive iodine after two weeks had elapsed, to determine whether the patient had any functioning thyroid tissue left. However, it was the opinion of the radiophysics department that, should the radiation be taken up by the thyroid gland, there might be sufficient radiation to destroy whatever function of the gland still remained. The child was therefore discharged from the hospital on Dec. 17, 1948, on the twenty-ninth postoperative day, to return two weeks hence for repeat serum cholesterol determinations. The serum cholesterol on discharge was 200 mg. per cent and the alkaline

phosphatase was 18 King-Armstrong units.

In spite of attempts to follow the patient, he was not seen again until March 9, 1949, when he was readmitted to the hospital. During the three months since discharge, the patient had not received any thyroid and the family stated that the child had been well, but had difficulty in eating because his tongue seemed to be getting larger. He was constipated, and glycerin suppositories had been given frequently. The weight was 13 pounds, 6 ounces, and the length was 23½ inches. In three months the child had gained 4 pounds in weight and had grown 2½ inches in length. The facies had changed somewhat. The child manifested a thick, protruding tongue, which was grossly and uniformly enlarged, puffy eyes, low-bridged nose, and a general apathetic appearance. The clinical impression at this time was hypothyroidism secondary to almost complete thyroidectomy. The serum cholesterol was 240 mg. per cent three and one-half months after the discontinuation of thyroid. This was a rise of only 40 mg. per cent over the level at the time of discharge. The serum alkaline phosphatase was somewhat low for this age, being 7 to 11 King-Armstrong units. Roentgenograms of the lower end of the femur and upper end of the tibia revealed the epiphyseal centers formerly present. The plasma bound iodine level was lower than 4 gamma, which is strongly suggestive of hypothyroidism.

Accordingly, on March 19, 1949, thyroid replacement therapy was reinstituted. One-half grain daily was given for five days; the dose was then increased to ¾ grain for six days, and then to 1 grain daily. On this regimen the child definitely improved. He took his formula much more avidly, he appeared much brighter, his tongue became smaller and his cheeks were less puffy, and his bowel habits improved. He had one stool daily without the necessity of suppositories or enemas. The serum cholesterol level dropped to 160 mg. per cent. The patient was discharged on April 10, 1949, the thirty-second hospital day.

The patient was last examined at 27 months of age. He was still taking 1 grain of thyroid daily. His mental and physical status were commensurate with his chronological age.

DISCUSSION

The preoperative diagnosis of extensive cystic hygroma of the neck was based in part on the clinical appearance of the lesion; the fact that congenital goiter is so rare in this region practically excluded it from consideration. Hygromas need not transilluminate, particularly if hemorrhage has occurred within the cysts. They may be a cause of mechanical distress. While usually unilateral, bilateral involvement has been seen, as well as involvement of the mediastinum and other parts of the body.[4] However, the firm consistency and anatomical distribution of the masses in the present case should have suggested the correct diagnosis.

In this case the diagnosis of congenital goiter was made after practically total thyroidectomy had been performed. Following surgery it was our intention to maintain the patient on thyroid replacement therapy. However, the parents did not follow the program outlined upon discharge of the patient, and no thyroid had been given for three and one-half months, when the patient was brought back to the follow-up clinic. By this time definite signs of hypothyroidism had supervened. The tongue was coarse and thick and protruded from the gaping mouth. The hair was sparse; the umbilical hernia was more marked. In addition, constipation

and failure to suck well were present. The clinical impression of hypothyroidism was not substantiated by the initial laboratory results. The roentgenograms revealed normal bone development for the patient's age, and two epiphyseal centers in the wrist had developed while the patient was not receiving thyroid replacement therapy. The serum cholesterol had not increased appreciably while treatment had been withheld. According to Wilkins[18] when thyroid medication is discontinued in hypothyroid children the serum cholesterol increases greatly in the course of four to twenty weeks, reaching levels 98 to 410 mg. per cent above those of the treated period. In normal children the rise is only 10 to 55 mg. per cent. The serum alkaline phosphatase was only moderately low for a 5½-month-old child, being 7 to 11 King-Armstrong units. The only chemical determination which was strongly suggestive of the diagnosis of hypothyroidism was the plasma protein bound iodine value of less than 4 gamma. Salter and associates state that a plasma protein bound iodine level of less than 4 gamma per liter is definitely subnormal and is of distinct value in confirming the diagnosis of poor thyroid function.[12] Two weeks after thyroid replacement therapy had been started, definite changes in appearance and behavior were noted. The child was last seen at the age of 27 months. He appeared physically and mentally normal and was still taking thyroid medication.

When the diagnosis of congenital goiter is made prior to surgical intervention, the application of iodine-containing ointments to the skin over the gland, plus the oral administration of iodine compounds, have been recommended. It is claimed that the goiter will frequently disappear after this treatment. On the other hand, Rienhoff has described rapid relief of dyspnea and cyanosis in a newborn infant with a very large thyroid, and grossly detectable shrinkage in the size of the gland after a few days of therapy with thyroxin administered hypodermically; in his experience iodine has been ineffectual.[11]

The most striking symptom in patients with congenital goiter other than the mere presence of the mass in the neck is the respiratory difficulty secondary to pressure on and displacement of the trachea. In the majority of the cases reported in the American literature respiratory obstruction was so severe that suffocation and death resulted. In cases where the respiratory symptoms are severe enough to produce dyspnea and cyanosis, emergency life-saving surgery must often be performed. Transection of the isthmus of the thyroid may afford relief from the mechanical obstruction in some of these cases. Because of retrolaryngeal extension together with compression in the tracheo-esophageal grooves, partial and subtotal thyroidectomy have often been required. It is felt that tracheotomy is less desirable in this neonatal age group than either of the other procedures described.

A summary of cases of congenital goiter treated surgically is contained in Table I. In each case respiratory obstruction required relief. Seven infants survived thyroid resection, in contrast to two newborn infants succumbing after tracheotomy. In one instance (D'Abreu[1]), left hemithy-

TABLE I. CASES OF CONGENITAL OBSTRUCTIVE GOITER TREATED SURGICALLY

CASE	AUTHOR	LOCALE	MATERNAL THYROID DISEASE	AGE AT OPERATION	SURGICAL PROCEDURE	SIZE OF RESECTED GLAND	PATHOLOGIC REPORT	RESULT
1	Peterson and Sondern,[10] 1911	New York City	Not stated	5 weeks	Subtotal resection	Horseshoe 6 × 4 × 3 cm. and 4 × 2.5 × 2 cm.	Adenoma and colloid degeneration	Good
2	Williamson,[19] 1933	New Orleans	None in 3 generations	18 months	Subtotal resection	25 grams	Diffuse adenomatous hyperplasia	Good
3	Symmers,[16] 1941	New York City	Not stated	6 weeks	Subtotal (4/5) resection	47 grams	Hürthle-cell tumor	Good
4	Davies,[2] 1943	Vancouver	Adenomatous goiter (untreated)	13 days (3rd goitrous baby)	Subtotal resection	6 grams	Subinvoluted phase of hyperplastic gland	Good
5	Morrow,[8] 1945	Chicago	Not stated	2 months	Part of each lobe plus isthmus	4 × 2 × 1.5 cm.	Hürthle-cell tumor	Good
6	Kunstadter,[6] 1948	Great Lakes	Not stated	Newborn	Tracheotomy	(Autopsy) 62 grams	Struma hyperplastica	Died
7	Seligman and Pescovitz,[13] 1950	New York City	Hyperthyroid (treated)	Newborn	Tracheotomy	(Autopsy) 16 grams	Hyperplastic gland	Died
8	D'Abreu,[1] 1950	England	None	1.1 month 2.3 months	1. L. hemithyroidectomy 2. R. hemithyroidectomy	4 × 3 × 2.5 cm. 4.5 × 3 × 2.2 cm. (14 grams)	Hyperplastic gland ♂ incipient involution	Good
9	Authors' case, 1948	New York City	None	7 weeks	Almost total resection	65 grams	Congenital diffuse parenchymatous struma	Good ♂ thyroid replacement therapy

roidectomy resulted in only temporary improvement, necessitating right hemithyroidectomy two months later before lasting relief was obtained. No reports of a fatality following thyroid resection for congenital obstructive goiter have been found. In at least three of the cases there was no evidence of maternal thyroid disease. There was no sex predilection. The possible significance of the diagnosis "Hürthle-cell adenoma" in Cases 3 and 5 is beyond the scope of this discussion.

Had the condition been properly identified in the present instance, a less extensive resection would undoubtedly have been preferable from the point of view of subsequent glandular function. Postoperative hypothyroidism was not recorded in any of the other surgically treated patients. Estimates of the normal weight of the thyroid in the newborn infant range from 0.7 grams[13] to 1½ to 2 grams.[1] The weight of the resected gland in the present instance (65 grams) is greater than that recorded in any of the patients treated surgically, as well as the autopsied cases summarized by Jones.[5] However, huge congenital goiters, resulting in severe dystocia and marked obstetrical difficulties, have long been recognized in the European goiter belts. McLanahan[7] delivered a stillborn fetus of a goitrous primipara; the fetal goiter measured 10⅞ inches in largest diameter.

SUMMARY

1. The incidence and clinical features of sporadic congenital goiter are presented.

2. A case of congenital obstructive goiter with surgically induced hypothyroidism in a 5-week-old child is described.

3. Criteria for proper diagnosis and therapy are discussed.

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A METHOD ADAPTED FOR THE DETERMINATION OF URINARY 17-KETOSTEROIDS IN CHILDREN

With Some Considerations of Interpretation

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THE development of extraneous co'or during the determinations of urinary 17-ketosteroids by the Zimmerman reaction has long been known and various methods for compensation have been suggested. Blank determinations on the urine extracts, in addition to reagent blanks, are used by some but these are not wholly satisfactory. When the concentration of 17-ketosteroids is low, as normally in the pediatric age group, the determinations are particularly unreliable since the difference in absorption at 520 mμ between the test and the blanks is small or inapparent. A modification of current methods has been devised for the determination of 17-ketosteroids in children with the object of attaining accuracy and simplicity. It is based on the Zimmerman reaction with appropriate blanks and carbon tetrachloride extraction of the final color.

Several means for the correction of extraneous color have been considered. Talbot and associates[1] have recommended the removal of nonketonic materials from urine residues by means of the Girard separation, since these comprise the greatest source of interfering colors. However, this procedure, while adequate, is time consuming and impracticable for the laboratory with limited facilities. Fraser, and collaborators[2] propose an equation for the correction of color, the validity of which has been questioned by Pincus.[3] In children, when the nonketonic chromogens far exceed the specific substances to be measured, this correction may be of little help.

Cahen and Salter[4] have shown that chloroform extraction of the final reaction removes the red color typical of 17-ketosteroids, leaving the extraneous brown pigment in the upper layer. The test solution is first diluted with 60 per cent alcohol. This principle has been applied to the present method because of its simplicity and effectiveness. Carbon tetrachloride has been used in the present method for the extraction of the undiluted solution and the mixture is briefly centrifuged. Reagent and residue blanks are included and similarly extracted. This has resulted in a very low absorption in blanks and quantitative recovery of known amounts of dehydroisoandrosterone.

The initial hydrolysis and extraction of urine specimens is carried out according to the technique of Drekter and co-workers[5] with appropriate readjustments of volumes for the concentrations of 17-ketosteroids in normal children. Provision for some flexibility has been made for those specimens containing high concentrations. Ethyl ether is preferred to other solvents for the initial extraction. It constitutes the upper level during extraction and facilitates the procedure since the lower

From The Children's Hospital of Philadelphia (Department of Pediatrics, School of Medicine, University of Pennsylvania).

level is repeatedly discarded. The validity of the hydrolysis and extraction is detailed by Drekter and associates.[5]

Aqueous potassium hyroxide is used to provide the alkaline medium for the Zimmerman reaction for two reasons: It is not subject to the instability of alcoholic solutions, although these may be preserved for a reasonable period of time by special means; ethanol and carbon tetrachloride are miscible, so that the final extraction would otherwise necessitate preliminary aqueous dilution of a medium of absolute alcohol. Aqueous 5 N potassium hydroxide is satisfactory as shown by Holtorff and Koch,[6] and in our experience it need not be rigidly titrated provided standards are included routinely.

REAGENTS

Absolute alcohol: 2 Gm. phenylenediamine are added to 1 liter of absolute alcohol. This is redistilled after standing three to four days.

Ethyl ether (absolute), reagent grade.

m-dinitrobenzene (Eastman Kodak)—purified by recrystallization according to Callow and associates.[7] A 2 per cent solution in absolute alcohol is prepared.

Potassium hydroxide (electroyltic grade): a 5 N solution in water is prepared and standardized to within 0.1 N.

Hydrochloric acid, concentrated (reagent grade).

Sodium hydroxide (reagent grade): 10 per cent solution in water.

Carbon tetrachloride (reagent grade).

Dehydroisoandrosterone:* used as the standard. A solution is accurately prepared in absolute ethanol so that 6 to 8 gammas of material are contained in 0.1 ml. Standard tubes numbered 1 and 2 are prepared in quantity by placing 0.1 and 0.2 ml., respectively, of the solution into them. These are evaporated to dryness and preserved for use with each series of determinations. Some provision for the prevention of evaporation of the standard steroid can be made, such as aluminum foil corking, since it is believed that loss may occur.

*Kindly supplied by F. E. Houghton of Ciba Pharmaceutical Products, Inc., Summit, N. J.

APPARATUS

Several separatory funnels having a capacity of 125 ml.

1.0 ml. pipettes graduated to 0.1 or 0.01 ml.

Erlenmeyer flasks.

Test tubes, 10 × 72 mm., which must be optically calibrated. These may be purchased (Coleman) or more economically, yet easily, calibrated in the laboratory.

PROCEDURE

Collection and Extraction.—

1. The total volume of a twenty-four-hour urine specimen is carefully measured.

2. A 20 ml. aliquot is placed into a 125 ml. Erlenmeyer flask to which 6 ml. of concentrated hydrochloric acid are added. If the total urine volume is 100 ml. or less, a 10 ml. aliquot is used. (This may sit overnight in an icebox.)

3. The urine is heated in a water bath at 80° C. for exactly ten minutes. It is then cooled in a tap water bath.

4. The hydrolyzed urine is shaken in a separatory funnel with 40 ml. of ether for exactly thirty seconds, with a pause at ten and twenty seconds to release pressure.

5. Following separation of the two layers, the bottom layer is removed and discarded.

6. The remaining ether extract is now shaken for exactly ten seconds with 15 ml. of 10 per cent sodium hydroxide and 15 ml. of water, respectively. The lower layer is discarded each time.

7. The remaining ether extract is drained into a small Erlenmeyer flask from which it is evaporated on a steam bath. *No flame.* The residue is preserved in the same (labelled) flask covered with aluminum foil. When several residues have accumulated, the colorimetric determination is conducted as follows.

Colorimetric Determination.—

1. Absolute alcohol, 1 ml. is added to each flask containing urine residues.

If an abnormally high level is anticipated, 2 to 4 ml. of ethanol are used.

2. A multiple series of three test tubes (10 x 72 mm.) for each determination is arranged in a rack, having been labelled by number to correspond to the respective specimen. Two tubes represent duplicates of the test, and one a color blank.

3. Two-tenths milliliter of the alcoholic solution of each residue is placed into each of three successive tubes, measured with a 1 ml. graduated pipette.

4. At intervals of sixty to ninety seconds (timed and consistent), each trio of tubes is treated as follows: 0.2 ml. of 2 per cent m-dinitrobenzene is added to each of the first two tubes, and 0.2 ml. of absolute alcohol to the third. Three-tenths milliliter of 5 N potassium hydroxide is finally added to all three tubes and these are immediately placed in a water bath at 27° C. which is shielded from light. With the beginning of the first trio of tubes, a timer is set at ninety minutes.

5. Following the last series of tubes, alcohol blanks and standards are similarly treated in duplicate. The alcohol blanks contain 0.2 ml. of the alcohol used, in addition to m-dinitrobenzene and potassium hydroxide as above. The same reagents are added to the standard tubes (Nos. 1 and 2) containing known amounts of dehydroisoandrosterone as described under "Reagents."

6. At the termination of ninety minutes, each series of tubes is removed at identical intervals in the order in which they were introduced into the water bath. Carbon tetrachloride is added quickly to the three tubes, 1 ml. into each, measured from a 25 ml. burette. Each tube is shaken exactly twelve times.

7. Following the carbon tetrachloride extraction, the tubes are centrifuged at 2,000 r.p.m. for five minutes. The lower layer now contains the specific color and the beam of the colorimeter will strike within its range. There is thus no need for separation of the layers. The color is stable for about twenty-five to thirty minutes, fading somewhat thereafter.

8. The optical densities of the specimens are read in the colorimeter set at 520 mμ.

9. The readings of the reagent blanks (average) are subtracted from all tests and standard readings. The specific color blank for each test is also subtracted from the corresponding average test reading.

10. A standard line is plotted with each series of determinations, based on the two standard readings, on plain graph paper. This should constitute a straight line through zero.

11. The value as read from the graph is converted into milligrams per day as androsterone (provided there were no deviations from the recommended volumes and dilutions) as follows:

$$\text{Value from graph} \times \frac{5}{4} \times \frac{\text{24-hour-urine volume}}{20} \times \frac{5}{1}$$

DISCUSSION

The described procedure is based on previous recommendations for simplicity[5] and specificity of color.[4] It has been adjusted to the requirements of the pediatric age group. The final carbon tetrachloride extraction has resulted in minimal absorption of blanks at 520 mμ so that the difference with the test solutions is greater. With the exercise of the precautions noted as to purification of reagents, the reagent blanks will be considerably less than 0.020 O. D. Test solutions will be within the range 0.050 to 0.150. When values are excessively and abnormally high, as in the adrenogenital syndrome, absorption will be great and test readings will fall into a less accurate area. This may be predicted in step 1 of the colorimetric procedure above and accordingly corrected; or one may use a smaller aliquot of urine if the clinical diagnosis warrants this. However, the excessively high level of 17-ketosteroids

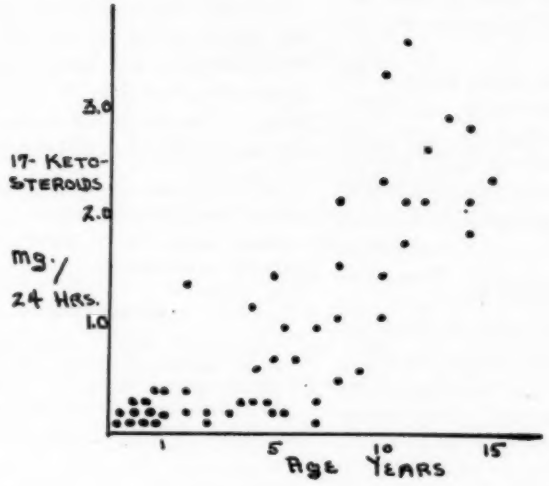
3.0
17- KETO-
STEROIDS
2.0
mg./
24 HRS.
1.0
1
5
10
15
AGE YEARS

Fig. 1.

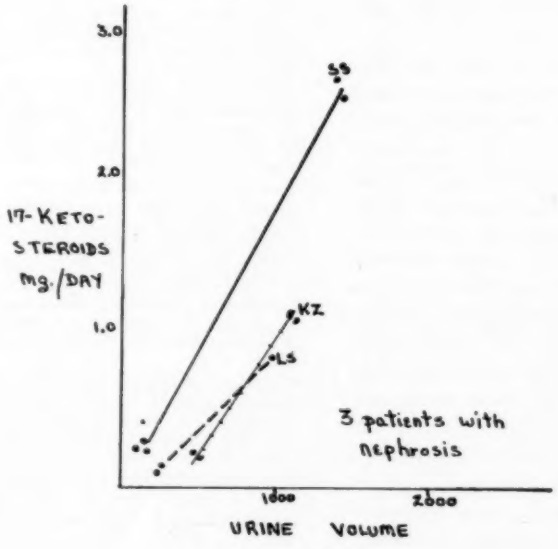
3.0
2.0
17-KETO-
STEROIDS
mg./DAY
1.0
SS
KZ
LS
3 patients with
nephrosis
1000
2000
URINE VOLUME

Fig. 2.

in a urine specimen is of diagnostic value, although the marked color development may lead to an error of ± 20 per cent.

Fig. 1 relates the daily urinary 17-ketosteroid concentrations, as determined by this method, to age. The relationship is similar to that previously indicated by Talbot and co-workers[8] except that some higher values are seen in early ages. Within some age groups there is a wide scattering. Rises with increasing age probably vary as do certain developmental physical characteristics within any age group. However, no correlation has as yet been drawn.

In our experience, one of the advantages of the method has been in the assessment of responses of children to adrenocorticotropic hormone. In the face of normally low levels, the rises effected with this hormone (the total of which may be less than 1.0 mg.) may not be significantly detected with less accurate techniques.

I[9] have previously stressed the relationship between the volume of urine and the levels of 17-ketosteroids under some circumstances. In conditions characterized by oliguria with bursts of diuresis (e.g., nephrosis and cirrhosis), marked variations may occur. This is illustrated (Fig. 2) in three children with nephrosis, several determinations having been indicated during oliguria and diuresis. The high levels with diuresis do not persist indefinitely. The possible mechanisms have been presented elsewhere.[9] It is believed that variations in urine volume constitute a serious limitation to the use of urinary levels of all steroids as a means of evaluating adrenal cortical function.

CONCLUSION

A rapid, simple, accurate method for the determination of neutral urinary 17-ketosteroids has been devised and especially adapted to the pediatric age group. Considerations relative to age and urine volume have been presented.

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The assistance of Dr. W. W. McCrory is gratefully acknowledged.

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Case Reports

INTRACRANIAL MALIGNANT NEOPLASM WITH ONSET BEFORE BIRTH

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INTRACRANIAL malignant neoplasm, with onset before birth, is a rare disease. In 1940 H. Gideon Wells[1] reviewed the existing literature and found only two such cases which he considered to be unquestionable.

The first case was that of Russell and Ellis[2] who described a polar spongioblastoma in a stillborn at term. There was a solid spherical mass in the left cerebral hemisphere associated with great internal hydrocephalus.

The second case as described by Wollstein and Bartlett[3] was a glioma sarcomatoides of the left cerebellar hemisphere. This tumor was manifest at the age of 2 weeks by hydrocephalus.

Wells found two other case reports of possible cerebral malignancy which he considered inconclusively diagnosed.

Since that review only one report of what appears to be a valid case has been found. This was Alper's[4] description of a tumor of the fourth ventricle associated with meningomyelocele and absence of cerebellum found in a 5-week-old infant.

A personal communication has been received from H. D. Palmer[5] concerning a sarcoma of the leptomeninges of the cerebellum in a 7-week-old infant with rapidly enlarging head since birth.

The present report is of a case of glioma, occurring in a newborn infant, and being manifest by a congenital hydrocephalus.

From Permanente Hospital.

CASE REPORT

W. D. was born at Permanente Hospital Oct. 7, 1950. The family history is noncontributory except that both parents and a sibling had a large head at birth and have had no subsequent evidence of disease. The pregnancy was full term and unremarkable except for a rather severe fall in the eighth month. Delivery was not traumatic. On initial examination, the infant weighed 9 pounds 2 ounces, and the only abnormality noted was a head measuring 15¾ inches in circumference, with widely separated sutures. He was a drowsy baby, regurgitated frequently, and took feedings poorly from the outset. Vomiting became projectile, and on the twenty-third day, x-ray studies for pyloric stenosis were made. These were normal. Skull films showed only separated sutures. On the same day, a subdural tap was performed and no fluid returned. This was followed by a left ventricular tap and free-flowing chocolate-colored fluid was obtained. The centrifuged fluid separated into three layers, a supernatant xanthochromic, then white, then dark red layer. A few unidentified cells were seen on smear. These did not resemble tumor cells. No Papanicolaou stain was done. No organisms were cultured. Sugar content of the fluid was 23 mg. per cent. Ventriculogram showed communication between ventricles. The lateral ventricles were moderately dilated with irregular outline. Studies for toxoplasmosis were negative.

Fig. 1.

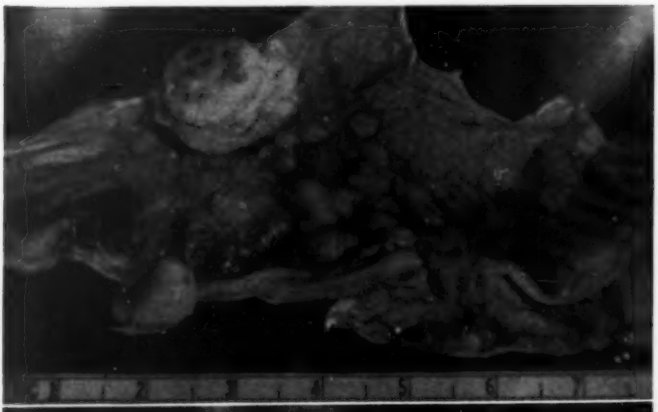

Fig. 2.

Fig. 3.

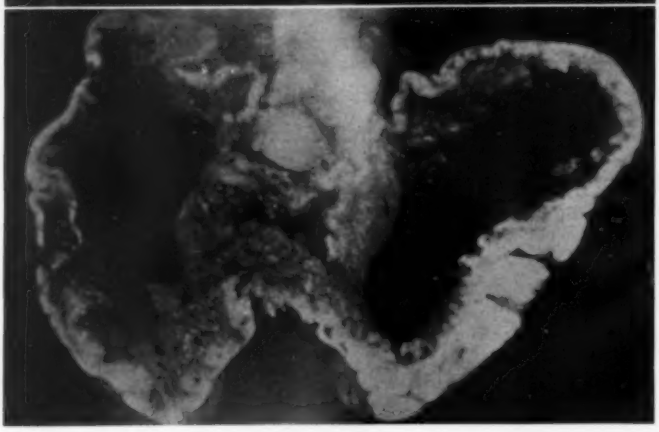

Fig. 1.—Meninges showing nodular metastases.

Fig. 2.—Brain viewed from ventral surface showing nodular tumor masses widely scattered.

Fig. 3.—Coronal section of brain showing widespread invasion of tumor and lining of greatly dilated ventricles with tumor tissue.

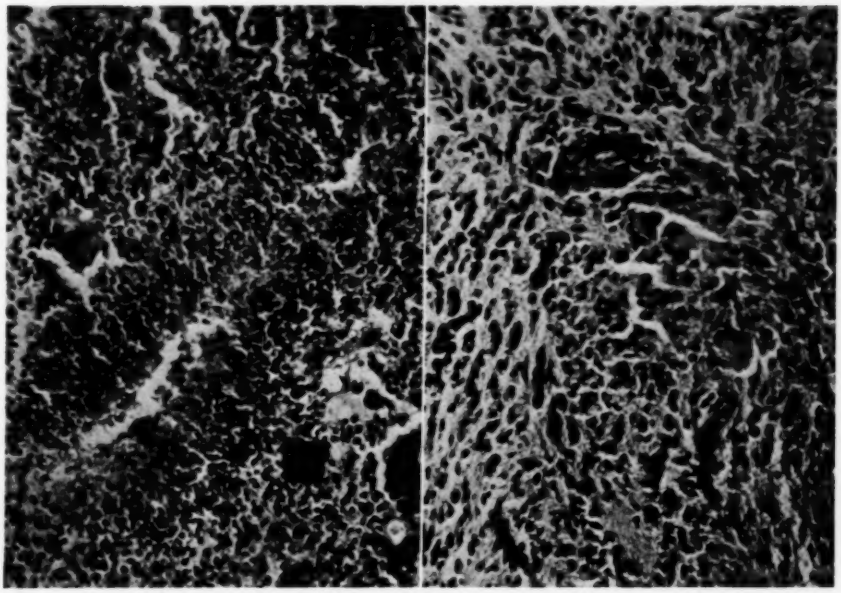

Fig. 4. Fig. 5.

Fig. 4.—Necrosis and palisading. (Hematoxylin and eosin, ×180.)
Fig. 5.—Giant cells and pleomorphism. (Hematoxylin and eosin, ×180.)

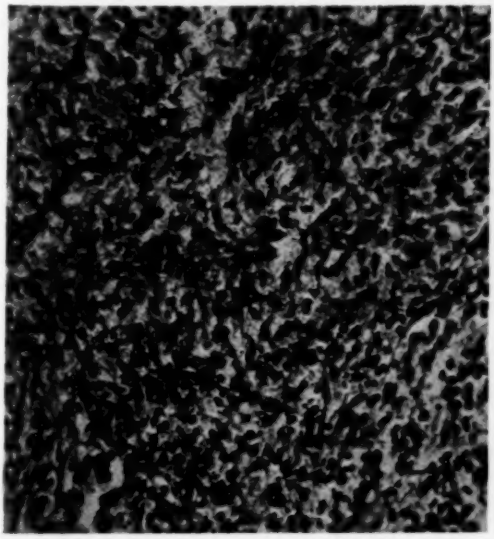

Fig. 6.—Spongioblasts. (Hortega silver carbonate stain, ×250.)

The condition of the baby became markedly worse on the twenty-sixth day when he developed Cheyne-Stokes respiration. This improved after a ventricular tap. Thereafter, such taps were repeated as intracranial tension increased. The fluid obtained continued to resemble the first specimen in appearance and no organisms grew on culture.

Poor feeding and vomiting persisted and the nutritional state rapidly declined in spite of supportive treatment. The head circumference increased to 17 inches. Intermittent fever occurred and no focus of infection was found. Antibiotics were given with no apparent effect. Eye grounds remained normal in appearance. Blood hemoglobin fell, and on the thirtieth day a small transfusion was given without difficulty.

On the thirty-third day the infant manifested decerebrate rigidity with marked opisthotonos and episodes of clenching hands and feet. Next day, lumbar and cisternal taps were attempted and no fluid was obtained.

On the forty-eighth day, a needle biopsy of the cerebral cortex was performed and the pathologist reported the presence of small tumor cells. On the forty-ninth day, the infant expired.

Autopsy Findings.—Careful search of the thoracic cage and its contents, the viscera, genitalia, and spinal cord revealed no tumor tissue.

The brain weighed 850 grams, with most of the enlargement confined to the cerebral hemispheres. Convolutions were flattened. Fleshy, pale, pinkish-gray nodules and plaques were numerous over the inferior surfaces of the brain, and some over the lateral and superior surfaces. They completely covered the optic chiasma and much of the brain stem and cerebellum. Several similar nodules were present on the dura mater, not attached to the brain. Coronal slicing of the brain revealed similar masses and nodules lining the entire ventricular system, with sufficient bulk to obstruct the foramina of Luschka and Magendie. The tumor had invaded and destroyed much of the basal ganglia and much of the white matter, periaqueductal gray matter, medulla, and cerebellum. The cerebral hemispheres were thin-walled sacs lined by tumor and filled with turbid brownish fluid, old blood clots, and soft necrotic fragments. It was impossible to determine the site of origin of the tumor.

Microscopic Description.—

"Brain: The tumor varied from place to place and shows a great variety of cell types. A few of these were identified with gold and silver stains as astrocytes and astroblasts, and a few others tended to form ependyma of a fairly mature type. The great majority, however, appeared to be bipolar, unipolar, and apolar spongioblasts. Primitive unidentified cells of various types were seen here and there. Some of the cells were of giant size with usually a single very large darkly staining nucleus and pinkish cytoplasm. Occasionally, the spongioblasts formed parallel rows, but most regions were very much mixed in pattern. Palisading with necrosis was seen very distinctly in a few regions. Endothelial and capillary proliferation was occasionally seen, as was coagulation necrosis. The tumor was highly invasive and showed no tendency toward encapsulation or circumscription anywhere. It invaded the choroid plexes and ependymal surfaces of the ventricle as well as other portions of the brain and meninges."

Final Diagnosis.—Glioma (probably glioblastoma multiforme). Reticulum was absent from the tumor, except for the dural metastases.

SUMMARY

A case of intracranial malignant neoplasm present before birth has been reported. A review of the literature has been presented.

CONCLUSION

It is concluded that this is a rare condition but should be considered in cases of congenital hydrocephalus.

The authors wish to thank Melvin Friedman, M.D., of the Department of Pathology, and Alexander King, M.D., and David Friedman, M.D., of the Department of Pediatrics for guidance in preparation of this report.

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FROSTBITE FROM PROLONGED EXPOSURE TO MODERATE TEMPERATURES

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FROSTBITE is usually described as a dermatitis and local tissue reaction resulting from short or prolonged exposure to extreme cold.[1, 2]

Experimental frostbite in laboratory animals using "moderate" temperatures have employed temperatures of 0° C.[3] The development of typical frostbite with local gangrene in a patient exposed to temperatures of 65° to 70° F. over a prolonged period of time seemed unusual enough to warrant reporting.

Fig. 1.—Well-demarcated gangrene of the helix of the right ear. Two months after exposure almost the entire area had sloughed.

CASE REPORT

F. D. is an 8-year-old Negro female admitted to Lincoln Hospital on Feb. 28, 1950, with a diagnosis of acute rheumatic fever and pneumonia. Six days after admission she went into acute and severe congestive heart failure necessitating constant oxygen therapy by Barach tent. Marked orthopnea kept her in an upright position, placing her right ear within six inches of the oxygen inlet. The patient was extremely restless and uncooperative and continually removed the protective head covering which was provided. As a result, her right ear was in direct and constant contact with a jet of air cooled to 65° F. After six days, the periphery of the pinna of the right ear was noted to be cold, blue, and nontender. The following day this area was a deeper blue and more sharply demarcated from the remainder of the ear. Edema and further demarcation showed during the next two days. At this time, the patient's general condition permitted the discontinuance of oxygen therapy. Within twenty-four hours, the ear became warm and tender. Vesiculation of the involved area was obvious by the tenth day. Following this, crops of weeping vesicles appeared. Scabs formed and were shed. Two months after the onset of the frostbite the major portion of the involved helix had sloughed.

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Since the first ice-cooled oxygen tent was described by Barach[4] in 1926, we have been unable to find a single case report of frostbite developing consequent to its use.

The helix of the ear has normally a very poor blood supply. The combination of this latter fact with the poor peripheral circulation in severe congestive heart failure and the prolonged and intimate exposure of the part to oxygen cooled to 65° to 70° F. was sufficient to produce the injury. Despite this relatively high temperature, capillary damage and exudation can apparently occur in a part with poor, sluggish circulation.

SUMMARY

A case of typical frostbite with gangrene of the right ear in a child with acute rheumatic fever and congestive heart failure is reported. The child's head was held within six inches of the oxygen inlet of a Barach type oxygen tent over a period of days. The temperature of the oxygen varied between 65° and 70° F.

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CALCIFICATION OF THE ADRENAL GLAND IN INFANTS AND CHILDREN

Differential Diagnosis and Report of a Case

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CALCIFICATION in the adrenal gland in infants and children is a rare finding and few cases have been reported in which this condition has been discovered ante mortem. In adults with Addison's disease secondary to tuberculosis, calcification of the adrenal is found frequently. However, the significance of adrenal calcification found early in life is often the source of much speculation. A case recently studied in this hospital has stimulated this report.

In animals Kruse[1] described bone formation in the adrenal gland of a female monkey in 1924, and Marine[2] in 1926 reported sixty-four cases of calcification of the adrenal in a series of 257 cats, all of which had distemper. This author also quoted a finding by Brüschweiler of calcification of the adrenal in fifteen cats in a series of 303.

Such adrenal calcification in infants and children has been described previously in only a few instances. In 1914 Rolleston and Boyd[3] observed calcification in the region of the adrenal glands in a boy aged 12 years with Addison's disease who died subsequently and was found to have had tuberculosis. Newsam[4] in 1924 found calcification and bone formation in the adrenals at autopsy in a female child aged 2 years 7 months who died suddenly within eighteen hours after the onset of convulsions and coma. This author quoted a case report by Victor in which the findings were practically identical, although there was no bone formation and the calcification was confined to the inner layers of the cortex.

In 1928 a case was reported by Gellerstedt and Hjelm[5] in which there was roentgenographic evidence of calcification above the right kidney in a boy aged 6 years. At necropsy a ganglioneuroma was found with calcific deposits. A large series of cases of hemorrhage into the adrenals of children was studied at autopsy by Snelling and Erb[6] and reported in 1935. Calcification was noted in two cases of the fifteen newborn group and in six cases of the twenty-three older children.

In 1943 Lintz[7] reported a case of a 13-year-old boy who had frequent convulsions due to hypoglycemia. Study of this patient revealed a flat glucose tolerance curve and bilateral adrenal calcification. The oral administration of glucose produced a complete remission of symptoms.

Alexander[8] in 1946 also reported the occurrence of bilateral adrenal calcification in a 6-week-old male infant with Niemann-Pick disease. The adrenal calcification was visualized radiographically and confirmed by post-mortem examination. A similar case with radiographic evidence of bilateral adrenal calcification was seen in an older infant with Niemann-Pick disease, but has not been reported.

CASE REPORT

L. H. (No. 314991), a 22-month-old white female child was admitted to City Hospital, Cleveland, on July 23, 1950, because of fever, limp, and pain in the left leg, all of one day's duration. Four days before admission the

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child had complained of some pain in the left leg after prolonged walking, but no abnormalities were noted by the mother. The child was referred to the Department of Contagious Diseases of City Hospital as a case of poliomyelitis and subsequently admitted to the Department of Pediatrics after initial studies had excluded this possibility.

The differential smear revealed 49 per cent polymorphonuclears, 45 per cent lymphocytes, and 6 per cent monocytes. The urinalysis was normal. The spinal fluid was crystal clear, under normal pressure, and without cells. The concentration of sugar in the spinal fluid was 57 mg. per cent and that of the spinal fluid chlorides was 123.7 meq.

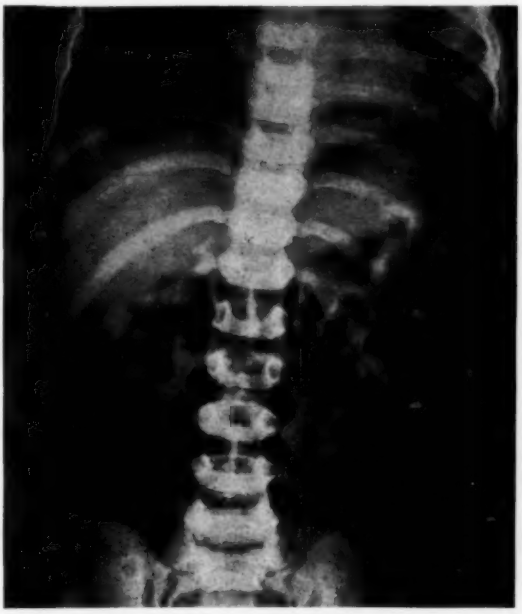

Fig. 1.—Radiograph of the abdomen showing calcification in the region of the right kidney.

The past history, as obtained, was noncontributory.

On admission, the temperature was 38.5° C. The positive findings included enlarged tonsils, moderate cervical adenopathy, gingival hypertrophy with bleeding, and shallow ulcerations of the buccal mucous membrane. Nothing abnormal was found in the extremities, but the infant refused to stand. The hemogram revealed 12 Gm. of hemoglobin per cent, 4.71 million red blood cells per cubic millimeter, and 8,250 white blood cells per cubic millimeter. The platelets and erythrocytes appeared normal.

A tentative diagnosis of aphthous stomatitis was made and the infant was given aqueous penicillin intramuscularly. The temperature was elevated and swinging for the first eight days in the hospital. Repeated examinations failed to reveal any abnormality in the lower extremities and no explanation for the initial complaint could be made. For this reason a skeletal survey for bony rarefaction and flat films of the abdomen and films of the chest were obtained. On the scout film of the abdomen, an area of increased density was noted in the region of the right adrenal (Fig. 1).

Intravenous urograms revealed no functional or anatomical abnormalities. A bone marrow smear from the sternum showed some bizarre small cells which were interpreted by some as possibly being neuroblasts. A bone marrow biopsy taken from the same area was normal. A diagnosis of possible neuroblastoma of the adrenal was made and surgical exploration elected.

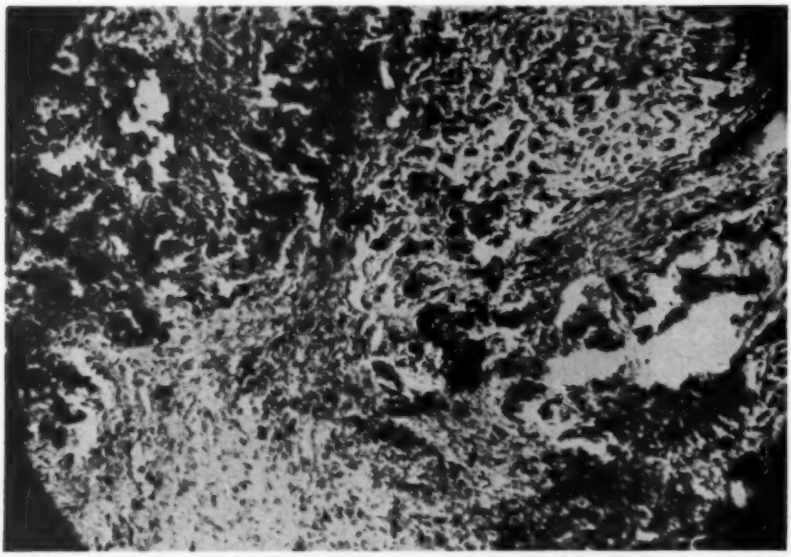

Fig. 2.—Section of the excised adrenal showing evidence of necrosis, hemorrhage, and calcification.

Operative Findings.—The right renal area was explored through a loin incision with excision of the twelfth rib. The kidney was normal in size and position. The adrenal was visualized and appeared normal in size, but it was obviously the seat of calcific deposits which caused grating on instrument contact. Total adrenalectomy was done without incident.

The patient made an uneventful recovery and was discharged on the sixth postoperative day. She has remained well to the present.

Pathology.—The adrenal measured 1.8 × 1.2 × 0.3 cm. Sections showed adrenal gland with a dense fibrous capsule. The normal architecture was distorted by large areas of old and recent hemorrhage and calcific plaques, many arranged concentrically. The final diagnosis was adrenal gland showing hemorrhage and calcification (Fig. 2).

Upon further questioning of the mother it was revealed that about six months prior to hospitalization the child had been severely beaten by the father and had complained for a time of some right flank pain.

DISCUSSION

Pathologic calcification usually occurs in tissues and cells which are the seat of disease. Foci of dense fibrosis, especially if hyalinized, and necrotic masses may become infiltrated.[9] Deposition has also been noted around foreign bodies, dead parasites, in thrombi and old hemorrhages. Some degenerative changes in certain tumors are also associated with calcific deposits.

In general, calcific shadows in the region of the adrenals are rare. In a study of 300 radiographs of people of varying ages free from Addison's disease and tuberculosis and with miscellaneous complaints, Ball[10] found only one instance of calcification. Seligman[11] found only four cases of calcification of the reticular layer in 1,185 autopsies in a hospital for chronic diseases.

The most common cause of calcification of the adrenal gland is the degeneration associated with tuberculosis in Addison's disease. Camp[12] found calcification in 32 per cent of thirty-four cases. In children, however, Addison's disease due to the destruction of the adrenals by tuberculosis is extremely rare.[13]

Hence, other etiological agents must be sought. Experimentally, Marine tried to reproduce calcification in the adrenals of cats in several ways. Sublethal injury, necrosis of the cortex by diphtheria toxin and arsenic, freezing the cortex with ethyl chloride, partial ligation, and trauma causing hemorrhage all failed to reproduce the lesion found in cats with distemper. However, hemorrhage into the adrenal of the newborn infant followed by calcification is well known. Calcification with hemorrhage into the adrenals has been found at autopsy in an infant only 8 days old.[6] In older children hemorrhage into the adrenals is seen with infection, and in Snelling's series there were five cases with calcification in patients who had died from intercurrent infection.

Certain tumors in the region of the adrenal also present calcification. Adenocarcinoma of the cortex has been described with massive calcification, one of the presenting features in a child 12½ years old.[14] Willis[15] states that in neuroblastoma and ganglioneuroma, degenerative changes affecting chiefly single cells or small groups of cells are common in the more malignant tumors of this group and this leads to fine granular, rarely massive calcification. Wyatt and Farber[16] found calcium deposits in six instances in thirty-four cases of histologically verified neuroblastoma sympatheticum in diverse locations studied roentgenologically. Pheochromocytoma is also known to present calcific shadows.[17] In one of Snelling and Erb's cases, calcification of the adrenal was noted in a child who had died with a tumor of the hypothalamus.

In the case reported, a scout radiograph of the abdomen yielded the evidence of calcification of the right adrenal. Perirenal air studies were not done because of the patient's age and the fear of such complications as air embolism, hematoma, and fat embolism.[18] Surgical exploration remains the method of choice for determining the status of the adrenal glands.[19]

Calcification in this case was due to old hemorrhage. Seligman mentions the possibility of extensive but sublethal hemorrhage at birth which might go on to calcification in the process of healing, but such calcification should be bilateral. In the case reported the calcification was confined to the right and probably secondary to trauma at the age of 16 months.

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Psychologic Aspects of Pediatrics

DISCIPLINE IN CHILDREN

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THE aims of proper child rearing are many. We strive for optimal physical health, for maximal intellectual development, for happy childhood, and preparation for happy and productive adulthood. But our efforts would be useless and our achievement empty did we not, at the same time, keep clearly in mind that the task implies more than bringing up children to be strong and to have fun. There are nobler attributes—honesty and love of truth, conscientiousness and devotion to duty, loyalty to ideals, dependability, consideration for persons and the opinions of others, regard for just authority, humility, courage and self-sacrifice, responsibility—without which life becomes meaningless and society chaotic.

These qualities are not acquired easily. Only through the sacrifice of immediate satisfactions can the child attain the nobility of spirit and the force of character in which a free society places its faith and alone can survive.

There are rules in a free society. They are not the rules established by capricious authority nor are they, for the most part, inscribed in legal archives. They are the self-imposed mores, the ethic, developed over a period of many centuries, which make possible social living in a free and gracious society. The principal objective of child training is to instil, through example and precept, these qualities; the principal function of discipline is to teach the easy acceptance of needful restraint.

Further, training and discipline are implements to direct the child's energies into useful and socially acceptable channels, to assist him in outgrowing less mature modes of behavior, and to curb excessive emotional demands. Training implies active encouragement, discipline implies restraint and, in addition, respect for and obedience to just authority.

THE NEED FOR DISCIPLINE

Permitting the child an outlet for his developing skills and feelings does not mean that he is to be indulged without limit. To pick up or rock the baby at the faintest whimper is hardly conducive to the development of a well-balanced personality. Such conduct only sharpens demands and leads to an egocentricity which is highly undesirable. The child reared without discipline has only a false freedom, for without the help of adult guidance and control he grows up uncontrolled and unsure of himself, un-

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certain of what to do and what not to do, slow in making decisions and angry when he has made the wrong one.

Proper child rearing requires a nice balance between encouragement for self-expression and freedom on the one hand, and training for conformity on the other. The child has his rights and privileges, but he has his duties and responsibilities as well. Too few restrictions, like too many, are undesirable. No one can say exactly where the dividing line is between these two. In fact we should speak of a "zone" rather than a "dividing line," and probably a fairly wide zone at that. It is a zone which permits considerable parental mismanagement without significantly injuring the child, provided he has been reared in an affectionate, sympathetic environment.

Man's nature is dual. He wants to break out and rebel against authority yet he finds comfort and real satisfaction in the approval of society which he gets from conforming. This conflict is apparent early in life. The young child wants to do things his own way and he will proceed on his own unless deterred; yet, while he is rebelling against restrictions, he expects his parents to stand for order. Even though he resists authority and is momentarily unhappy when crossed, failure to curb his activity altogether leads to confusion and even greater unhappiness.

In many instances the child's resistance to direction is not so much a revolt against authority as an effort to carry out his own plans without interruption or interference. The child should be permitted to experiment and to act on his own initiative to the extent that he is intellectually capable, but his conclusions should be reasonably controlled. He needs increasing freedom as his legitimate needs and capacities grow, but this freedom must be limited by his ability to take responsibility. As he matures he may be told the reasons for restrictions and the consequences which might result from transgressions. He should be encouraged to use his own judgment wherever possible, but this cannot be done without direction and guidance. Turning the child loose does not make him independent.

Recent decades have witnessed a striking change in prevailing ideas regarding the rearing of children. The strict discipline of earlier days, based on religious principle and social custom, has been replaced by a laissez-faire attitude. The reasons for this change are many: the loss of influence of formal religion; the popularity of psychoanalysis with its emphasis on the dire effects of frustrations and inhibitions; the centering of attention on emotional development to the detriment of spiritual development; the false doctrine that mistakes in child training register themselves permanently in the child's psyche and the consequent loss of parental self-confidence and, with it, authority; two world wars; and a clearer but as yet incomplete understanding of the principles underlying child rearing. In addition many parents are unwilling to make the effort necessary for proper discipline. They find it easier to give in; in addition, especially with older children, they fear inviting the child's resentment.

The attitude that a child's behavior should be completely unrestricted and that he should discover for himself

what is and what is not desirable behavior is unwise since it requires the child to make decisions for which he lacks mental power and experience. The child may find out to his sorrow; and he may react with resentment toward his parents because he was not warned beforehand of the unwisdom of his behavior.

Discipline is necessary for instilling knowledge of the social amenities and for teaching respect for the property of others. Many customs are observed for no reason other than that it is usual to act in a certain way. Little is to be gained by fabricating explanations. For example, the child soon learns that it is not because he will cut himself that he must not eat with his knife. It is much better to say that certain things are not customarily done and therefore the child may not do them. There is no reason for this except that society, of which he is a part, does not approve. The similarity with certain tabus which children have among themselves may be pointed out. For example, children do not tattle on each other, they do not run to mother crying, and so on.

Situations sometimes arise in which there must be immediate, implicit obedience. These are, for the most part, situations which concern the child's safety. The child should understand what these are and why he must obey at once without question. He will soon learn that a certain tone of voice or a certain word from the parent such as "Stop" or "Be quiet" must be obeyed. This should be made automatic. The number of these prohibitions should be few but they must be rigidly adhered to.

It is not enough to bring up a child to behave properly simply because he knows that otherwise he will be punished. He must be able to distinguish between what is considered proper and improper behavior and he needs to be able to restrain his impulses even though no punishment is threatened. He must also be able to sacrifice immediate pleasures without being continually admonished to do so. The well-disciplined person is one who can accept his obligations to himself and to society easily.

The disciplinary attitudes of parents will depend to a large extent on the innate endowment of the child, the aims and personalities and cultural backgrounds of the parents, and the type of society in which the family lives. It is reasonable to assume that children vary in their innate capacity for emotional expression as they do in all other measurable attributes. Differences in the degree of aggressiveness or submissiveness are evident early in life. The aggressive child will require more curbing than the naturally submissive one.

Parents, too, differ in respect to their ideals and personalities and cultural backgrounds. Some parents, out of intense affection for their offspring or because of the manner in which they were reared, prefer to give their children a maximum of freedom; others, perhaps equally affectionate but more concerned about the unbridled behavior and aimless ways of many young people, choose the tighter rein.

The character of the society in which a child is reared is an important consideration. Discipline is meaningful only in terms of the culture for which it is designed. It would be unwise to bring up a child

to the nobler attributes necessary for social living in a free community if it were his lot to live in a coercive society where success depended on submission to governmental stringency.

AUTHORITY

In the normal course of events the child first experiences discipline through authority imposed upon him by his parents. It is unfair to expect the 2-year-old child to discriminate between the things which he may touch and those which he may not. Moreover it is comforting to him, as it is to the adult, to know the limits within which he may exercise his freedom—provided that the limits are wide enough to give ample scope for his desires.

Authority which is firm, kind, reasonable, and consistent gives the child that sense of security which is essential for his emotional development. Parental hesitation and discussion often lead to negativism and aggressive behavior. In the administration of disciplinary measures a sense of humor in the parents and child is invaluable.

By learning to accept authority the child acquires the ability to suppress his impulses and to forego immediate pleasures for some future desirable goal. Such behavior is necessary throughout life. Whether the task be to learn a trade or a profession, or to keep a promise, one must be willing to make the necessary sacrifices for the ultimate desired aim.

The effectiveness of authority is diminished by its too frequent or improper use. Some children are cowed by an overauthoritative parent and respond with submissive behavior and lack of initiative. Others, less pliant, express their resistance in one of several ways: by a general slowdown in their response to commands, e.g., dawdling, "not hearing" commands, "misunderstanding" or "misinterpreting" demands; by evasive behavior, that is, by misbehaving on the sly; or by open rebellion. Whatever the immediate reaction, these children tend to develop resentment toward all authority; and they come to attribute their own personality deficiencies to the early parental mismanagement.

DISCIPLINARY PROBLEMS

Disciplinary problems arise when the parents expect implicit obedience; when restrictions are too numerous; when demands on the child are unreasonable and beyond his comprehension, as when a small child is expected to keep a promise; when parental demands are inconsistent and unpredictable; when parents are overpermissive; when the parents lack a sense of authority; when the household is unordered; when the standards within the home differ from those of a group as a whole, as when foreign-born parents try to impose the standards of their own childhood on their children. In a certain number of cases the complaint of misbehavior is simply an expression of parental hostility to the child.

Many children misbehave for the sole purpose of getting attention. Some are overprotected children who require excessive amounts of attention, while others are rejected children whose only means of calling attention to themselves is by misbehavior. A certain number of children, uncertain of parental affection, misbehave to test the parental reaction. In occasional instances the child feels

guilty, for one reason or another, and misbehaves in order to invite punishment.

In many instances, especially among city dwellers, disciplinary problems arise because the home is too small to permit the freedom of motion which a young child needs, and outdoor activity is restricted owing to lack of space. There is no place to keep objects of value where they will be out of the child's reach. He must be continually admonished not to handle various objects and to be quiet lest he disturb neighbors and, naturally, he rebels. Under favorable circumstances the child, when emotionally disturbed for any reason, finds an outlet for his hostile feelings in physical activity and play. This is not possible in the pent-up existence many children are forced to live.

DISCIPLINARY TECHNIQUES

Disciplinary action, in order to justify itself, must serve a useful purpose and should not be made to serve as an outlet for the disciplinarian's offended sense of dignity or as an emotional release for the parent. The purpose of discipline is not to make the child obey. The parent must learn to accept failure and poor behavior on the part of the child without feeling personally thwarted. "He can't get away with that with me," is not an adequate reason for disciplinary action. "I was so upset when he didn't fight back that I gave him a good shaking" relieves the parent's annoyance without teaching the child to defend himself.

The relationship between the parent and child must not be jeopardized by the method of discipline and the parent should avoid vindictiveness and resentment. The attitude of the parent should be reasonable and not arbitrary. In so far as discipline involves frustration or deprivation it is important that it be made emotionally acceptable to the child by giving adequate reassurance of affection and concern.

Ridicule and sarcasm are to be avoided since they take unfair advantage of the child who is unable to reply because of his limited mental development and his fear of reprisal. They arouse resentment and antagonism.

The mental functioning of the young child is almost entirely on a concrete level and abstractions such as "right" and "wrong," causation, aesthetic considerations are beyond his comprehension. It is, therefore, useless to make explanations which he cannot grasp. Behavior in young children is largely conditional. Authority must be accepted without question since explanations are meaningless, if not confusing.

Even young children differ in the amount and type of indulgence and deprivation they can endure. This difference is dependent on the personality make-up of the child, his developmental status, and on the kinds of relationship set up between him and the parents. As the infant relinquishes demands on his parent and learns to accept frustration he gets substitute satisfactions from the world about him through play. He becomes less demanding and more willing to accept direction. Both control and permissiveness are valuable in meeting the child's needs.

Frank and friendly discussion from early childhood help to bring hidden feelings of aggression to the surface.

The child's inner struggles should be exposed and not repressed. In this way feelings of guilt and shame may be relieved and the need for misbehavior avoided. An atmosphere of easy give and take in the family aids the child in directing his aggression into acceptable channels.

As the child matures he must learn, all along the line, that he is a member of an orderly household where adjustments to the convenience of others are mutually necessary. Praise for good behavior is a much better training procedure than disapproval for bad, but both are usually necessary.

Discipline, if it is to be successful, that is, if it is to lead to easy acceptance, implies on the part of the parents an awareness of and respect for the child's maturing needs. During the second year of life, when the child is beginning to interest himself in his environment, his curiosity and eagerness are liable to lead to behavior which runs counter to the convenience of other members of the household. He wants to touch and manipulate whatever he sees. In this way he learns to distinguish objects and their qualities and acquires an enormous amount of basic information. It would be a great mistake to interfere with this learning process; yet a child cannot be permitted to learn what fire is by burning himself, nor what glass is by breaking a favorite ornament. Harmful and valuable objects can be removed from the child's reach and this should be done whenever feasible. But this is not always possible, or desirable, and a certain amount of control is therefore necessary. The child must learn to have consideration for others and for their property. Disciplinary problems generally begin during the period of emerging self-dependence.

Offering substitutes, e.g., offering a favorite toy when the child wants to use his crayons on the wall, is of little use as a training method. In the example given it may save the wall temporarily, but it will not prevent the child from returning to it unless the parent has, before offering a substitute, shown disapproval of the original behavior.

Discipline should be consistent. The child should understand clearly what he may not do and, if he is old enough, he should know why. He should know, further, that if he transgresses he will, inevitably, invite parental disapproval. It is confusing to the child to be permitted something on one occasion and to be refused the same thing at another time depending on the mood of the parents. Inconsistent stimuli produce neuroses in animals: and it is reasonable to assume that they do likewise in human beings.

Both parents (and grandparents) should be consistent in their behavior toward the child. When one parent takes a stand on a disciplinary situation the other parent must back up this stand. Otherwise the child is likely to do as he pleases—and be unhappy. There is no one right way for a child to behave. When differences of opinion on discipline arise between parents, the chances are that either parent's approach would be satisfactory. Parents will do less harm by agreeing to an error in discipline than by disagreeing between themselves in the child's presence. Parents who are mutually hostile often compete for the child's favor by canceling the other's disciplinary

measures. They argue about his behavior in his presence and he quickly learns to play one against the other. As a result he comes to hold authority in contempt, not only in the home but in the outside world as well. Parental difference of opinion regarding a child's behavior is one of the most potent causes of poor discipline.

Under certain circumstances parents are necessarily inconsistent in applying disciplinary measures to their children. The sensibilities and aggressive impulses of children vary. The less sensitive, more wilful ones will require more curbing than the others. An older child may need to be reproved for an act, while his younger sibling is excused. Coming to breakfast with hair uncombed and shoelaces untied is quite all right for the 6-year-old but his 12-year-old brother should be expected to take more responsibility for his appearance.

Invidious comparisons are useless as a disciplinary technique. They lead not only to antagonism toward the parents, but to antagonism toward the one with whom he is compared, usually a sibling or schoolmate.

EXAMPLE

The behavior of young children is determined to a large extent by example, by precept, by rewards, and by punishments. Only later on, as the mental faculties mature, do reason and ethical concepts become meaningful. By far the most important influence is the example of the parent. It is the ever-present model on which the child fashions his behavior. Given a friendly, affectionate, consistent atmosphere, children will be truthful or deceitful, conscientious or lax, well controlled or impulsive, orderly or slovenly, according to the behavior of the parents. If, however, the child is unloved and resentful he may reject the example of his parents and behave in a manner which he knows will annoy them.

REWARDS

In animal experimentation the two conditioning methods used are rewards and punishments. The rat learns to solve the maze because he gets the cheese only when he follows the correct path. In human beings, similarly, behavior which brings satisfaction and approval is retained and elaborated and behavior which brings failure, discomfort, or disapproval is discarded. This applies to the random movements of the infant as well as to the adolescent's behavior on his first "date."

The most desirable reward for the child, from the viewpoint of training, is the approval of the parents. Every child needs and is entitled to this parental expression. Conversely the parent will show his disapproval for conduct which he wishes to discourage. Later on, the approval of teachers and friends assumes increasing importance, and, still later, there is the inner sense of satisfaction and achievement which comes from a task well done and the attainment of just reward. The wise parent will use this method from the very beginning to instil into his child those virtues which he cherishes. He will show his pleasure by words and smiles and by pointing out how the child's position in the group becomes more important because of improved social conduct.

In showing approval and admiration it is important that the type of

behavior be stressed, rather than the child. In this way the child learns to take delight in his achievement rather than in himself and he learns to do a good job rather than to be personally admired.

In general, material rewards like toys and money are of little use as training methods. They may supplement parental approval but are in no way a substitute for it. Promising a material reward for good behavior gives the child the choice of not behaving.

PUNISHMENTS

Punishments are used in child rearing when other techniques fail to deter undesirable behavior. The need for punishment means that discipline has broken down. Since neither training methods nor children are perfect, punitive situations will arise from time to time. Under ordinary circumstances such occasions will be rare; if they are frequent something is wrong with the training procedures. If the child learns early in life that misbehavior invites discomfort or disapproval, whereas desirable behavior is appreciated, he will soon come to behave in an acceptable manner.

Much self-control cannot be expected of a young child. He should be protected against temptations until he has matured to the stage where he may be expected to resist them. For example, he should not be asked to make promises. He is incapable of remembering directions for long periods of time, and often, if he forgets and breaks his promise, he is scolded both for disobeying originally and for not keeping his word. A young child does not comprehend the meaning of honor or trustworthiness.

Young children are fundamentally truthful and usually admit their transgressions readily. Only later do they learn that they will be punished if they are found out but will escape if their misconduct is not discovered. The parent should be careful to avoid situations of this sort. It is preferable to give a certain amount of credit and even lighten the punishment if the child is honest enough to admit what he had done.

When a child is known to have done something naughty it is unfair to "test" him by asking what he has done and trying to make him admit it. It is far better to simply tell him that he has transgressed. Asking encourages evasion especially with certain children who are so inclined. In such instances it is wiser to overlook a transgression when one is not sure rather than to invite a falsehood by questioning.

The threat of withdrawal of affection as when a parent says, "I won't like you any more if you do so and so" is both unwise and unfair, since it exploits a desirable relationship.

Ordinarily the first offense should be punished if the child is aware of his fault. Punishment involves pain and, to be effective the pain inflicted must be greater than the pleasure derived from a given act. After the child has been punished he should be accepted into the family group again as though nothing had happened. He should not be made to feel continued disapproval and no further reference to the previous misbehavior should be made as this may give rise to feelings of inadequacy, guilt, and rejection. If the misdemeanor is repeated the punishment should be more severe than the first time, but there should

be no threat of future punishment. Little is to be gained from this and a sensitive child may be seriously frightened. The child should know what is expected of him, that it is to his advantage to behave in a certain manner, and that if he disobeys he will surely be reprimanded. Threats give the child, to some extent at least, the choice of committing the misdemeanor and taking the punishment or of behaving properly. Moreover, it may not be convenient for the parent to carry out a particular threat and, in such a situation, the child feels that he has been able to get away with misbehavior and will be tempted to try again. In this instance, too, confidence in the parent's word is shaken.

Threats of punishment by the father later on lead not only to dread and dislike of the father but give the child ample time to become fearful and anxious over the type of punishment he may receive and to plan ways of escape or revenge.

Frequently the child is threatened with something or someone with whom he may have contact at another time, such as the hospital or the doctor, and when he must go to the hospital or meet the doctor he experiences intense fear. Such threats are patently unwise.

Punishments, like rewards, should be depersonalized. It is the act, not the child, that is wrong.

The punishment should fit the intellectual and moral development of the child. During the early years it should be immediate, mild, and of short duration. In a sense, a punishment is "face saving." It is comforting for the child to know that he has paid for his transgression by being punished. It cancels out the situation. Explaining that he has behaved badly and then not doing anything about it may have the same effect on a sensitive child as shaming him and making him feel guilty. Occasionally young children try to punish themselves by hiding in a closet, asking to be spanked, and so on.

Suitable disciplinary methods at this early age are a sharply enunciated "no," a look of disapproval, or a light slap on the hand. These act as conditioning stimuli just as the loud noise of falling dishes or a burn on the hand from a hot radiator will inhibit action the next time the young child reaches for the tablecloth or puts his hand near something hot. If the parent maintains an affectionate, understanding attitude even while voicing disapproval, there will be no little chance that feelings of revenge and resentment will develop.

Corporal punishment has limited usefulness as a disciplinary technique. An advantage of spanking is that it is readily understandable to the child since he himself would react in this way. On the other hand, it encourages him to continue to hit out when the occasion arises; also some sensitive children react with an offended sense of dignity and resentment. In general, spanking is inadvisable. Except for the purpose of giving a conditioned response in a young child it has no place as a disciplinary technique. Having a very young child stand in the corner for two or three minutes is usually sufficient punishment for any offense at this age.

After the first two or three years the most effective punishments are scolding, deprivation of privilege, and isolation. The advantages of these

methods are (1) no physical pain is involved, (2) the duration and severity of punishment may be varied, (3) there is no long period for the child to feel abused and to plot revenge, (4) when the punishment is over the child may be reinstated in the family circle, and (5) the parent's personal feelings are not involved. If the child is old enough he should be made to understand why the act which he committed was undesirable and therefore punishable. When the punishment is over there should be an immediate clearing of the atmosphere.

When isolation is used as a punitive measure it should be made clear that the intent of the punishment is removal from the group because of antisocial behavior. No emphasis is put on the place of isolation and the parent should not threaten the child with confinement in any particular place. He should not be confined to his room as this may condition him unpleasantly against a place which he should enjoy and where he should feel free. Similarly, sending the child to bed is a poor form of punishment since rest and bed should be pleasant with no unhappy associations. Nor should the child be isolated in any place where he may be afraid such as an attic, a lonely room, or a closet, since this may intensify already present fears and give him an undesirable emotional shock. He should not be left alone long enough to meditate on methods of revenge. The parent should take the initiative and invite him to return to the group, assuming that he is going to behave. There should be no threat of desertion by the parents.

At 4 or 5 years of age it is usually possible to reason with children but it is undesirable to establish the custom of prolonged discussions over misbehavior. A clever child often takes advantage of the parent who uses these techniques. In the course of the conversation the central issue is obscured and the disciplinarian finds himself discussing totally unrelated matters. Many children enjoy the added attention obtained in this way and so continue the discussion beyond all reason. Silence on the part of the parent is often successful when talking is an obstruction. Little is to be gained by trying to reason with a child immediately after he has been punished and it is valueless to insist on repentance, because, when forced, it is seldom sincere. It is often preferable to let the child "save face." Persuasion is a poor method of discipline.

Whenever possible the type of punishment should be related to the nature of the misdemeanor. Thus it may be pointed out that immature behavior is punished by deprivation of some more grown-up privilege.

One must be careful that overseverity does not discourage initiative. A child may have good reason for misbehaving. If he is improperly placed in school and therefore unhappy it is easy to understand why he dawdles while dressing, fusses about breakfast, and is late in getting to school. A different class, remedial reading, or transfer to another school may resolve the difficulties entirely. It is important to try to understand the child's point of view, so that he will not feel that he is misunderstood and unjustly punished.

If the child can be taught that life is pleasanter when he is well behaved

than when he is naughty, he will soon come to understand the advantage of proper conduct. Many disciplinary problems should never have been allowed to occur. When the parent is inconsistent the child may do something which is not acceptable without realizing it. Thus he may be sent to the movies one day to get him out of the way while his mother is busy, and the next day, if he goes, he may be scolded for not staying at home and keeping her company. When the parents disagree about what the child may do, he naturally follows the commands of the one whose ideas more nearly fall in with his own, thereby disobeying the other parent. When important and unimportant transgressions are treated by the parent with equal severity the child frequently becomes confused and discouraged and assumes an attitude of not caring and carrying out his own ideas without regard to the disapproval of his parents. Parents who lack self-confidence and are unsure of themselves are often unduly severe in the punishment of their children.

Situations should not be created which will tempt the child to misbehave. It is unfair to leave candy and money about in order to see if the child will take them without permission, nor should the mother say she is going out and then come back to see what her child is doing. The child who is surrounded by rigid restrictions and rules is more likely to be disobedient than one who is given a certain leeway and is controlled by a few reasonable rules which he can understand.

The child's life should be viewed as a whole and discipline should be such as to accomplish what one wishes in the long run. In this way nagging can be avoided and the whole plan of training made clearer to the child. Thus punishment for an unsocial act may be dispensed with if the child shows an understanding attitude toward his transgression and why it is being handled in a particular way by the parent.

During the adolescent period the parents should be especially careful not to magnify the importance of minor infractions of rules. The adolescent is likely to be critical, argumentative, and unsure of himself and, when disagreements arise, he often blames both himself and his parents. Feelings of unworthiness are common at this age. The parent should commend good behavior and proper attitudes and should try to make clear the aims toward which he is striving.

Deprivation of privileges is the only punishment which has any value at this age and this should be used only occasionally and with care. Withholding the weekly allowance is a poor method of punishment. This should be regarded as the child's right and should not be tampered with. The advantage to the child of being trusted and not watched by his parents should be stressed. He should understand that his parents wish to help him fit into society and are willing and eager to adviser him about behavior which will make this easier for him. Discussions about behavior in general, when there is no particular point in mind, will help the child to formulate his own ideas on the subject and will aid him in reacting suitably when such situations arise. Withdrawal of approval is severe punishment, and should be used with care in the adolescent.

Cole has listed five outstanding characteristics of proper punishment for adolescents:

Whenever possible the type of punishment should suit the transgression. Thus the natural punishment for a boy who, in anger, throws an ink well at the wall is to make him clean it up—not to require him to solve six extra problems in algebra after school. Second, punishment must be certain. To punish a child one day for poor behavior and to let him go scot-free at another time for the same behavior is too variable to be effective. Third, punishment should be just. Petty as well as unintentional misbehavior should be overlooked. Fourth, punishment must be impersonal. The disciplinarian must not use punishment to relieve his own exasperation. Lastly, punishment should be constructive and aim at better self-control.

UNDESIRABLE DISCIPLINARY TECHNIQUES

Disciplinary techniques to avoid are as follows:

Threats of withdrawal of affection since it jeopardizes the relationship between parent and child.

Invidious comparisons which lead to antagonism toward the parents and toward the one used for comparison.

Ridicule and sarcasm since they take unfair advantage of the child and arouse resentment and antagonism.

Belittling, which may lead to loss of self-confidence.

Inconsistency, which only confuses the child.

Prolonged discussions and reasoning.

Harping on a misdemeanor after the punishment has been meted out.

Prolonged punishments.

Excessive disapproval which often discourages initiative.

Corporal punishment.

Deprivation of those things which may be considered the child's right—food, companionship, money allowance.

Threats of future punishment which make the child unduly apprehensive or which are frightening to the child.

Bribes which give the child the choice of complying or misbehaving.

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Comments on Current Literature

HERPANGINA

DURING the period from 1917 to 1924, John Zahorsky described a distinct and rather characteristic clinical entity to which he gave the designation herpangina. Since that time, at least three reports of similar outbreaks have appeared in the medical literature. The last and most complete study was reported in the *New England Journal of Medicine* (August 23, 1951). Parrott, Ross, Burke, and Rice, who worked in collaboration with Huebner and his associates, present in this issue a detailed discussion of herpangina, and include in their report an interesting account of the extensive virus investigations carried out at the National Institutes of Health.

Herpangina is a summer illness which may occur in children in the age period from 6 months to 15 years. In the majority of cases reported, however, the patients were less than 10 years of age. The condition is thought to be a distinct clinical entity, is a common summertime malady in childhood, and has a widespread distribution throughout the country. The disease is characterized by relatively sudden onset and high fever for from one to four days. Anorexia and dysphagia have been described as frequent symptoms, and sore throat is considered a common complaint, particularly in the older child who is able to report discomfort. Headache and generalized muscle pain have been noted very infrequently, and the absence of diarrhea has been a consistent finding. A cardinal manifestation of herpangina is the presence of grayish-white papulovesicular lesions, 1 to 2 mm. in diameter, noted in most cases on the anterior pillar of the tonsillar fauces. The lesions which appear first as discrete vesicles, surrounded by an areola of erythema, eventually rupture, assuming the character of ulcers with grayish-yellow coloration. Diffuse injection of the pharynx is usually present, but no follicular exudate is reported as a rule. In the majority of patients, the findings are limited to the throat, and the remainder of the physical examination is negative. Other respiratory manifestations such as cough, rhinitis, and otitis media are conspicuous by their absence. The disease has a benign self-limited course, usually of two to four days' duration.

In general, routine laboratory studies are without distinction, except that approximately one-half of the patients reported have shown a definite leucocytosis, a finding considered of some interest in view of the virus etiology. Treatment of the condition has been entirely symptomatic. About half of the patients reported in this series received penicillin during the acute stage, with no significant change in the clinical course of the disease. No serious complications have been reported.

Careful clinical observations made over a period of years by Parrott and his associates had emphasized the fact that this disease had been occurring during the summer months in the District of Columbia with considerable regularity. Consequently, when an epidemic occurred in July and August, 1950, careful, complete clinical and laboratory studies could be initiated at once. Twenty-two patients ranging in age from 6 months to 8 years were included in the study. Of singular interest in the series was the relatively high incidence of the disease in siblings, eight of the twenty-two patients being siblings.

On the basis of the clinical observations, these authors stress the likelihood of diagnostic confusion between herpangina and herpetic gingivostomatitis. Table 2 from their report summarizes admirably the characteristic features of both these common pediatric entities. Such tabulation focuses attention on the distinct, char-

TABLE 2. HERPANGINA AND HERPETIC GINGIVOSTOMATITIS

CONDITION	ETIOLOGY	AGE	SEASON	NATURE OF ONSET	DEGREE OF FEVER (F.)	CLINICAL FEATURES		
						PAIN	PHARYNGITIS	OTHER SIGNS AND SYMPTOMS
Herpangina	"H" virus (Group A Coxsackie viruses)	1-7 (occasional adult)	Summer only (occurs in epidemics)	Sudden	100-105	Mild in oropharynx	Inflammation	"Sore throat," vomiting
Acute herpetic gingivostomatitis	Herpes virus	1-7 (but adult as well)	Year round Most in winter (not in epidemics)	More gradual	100-103	Severe in oropharynx	Not often involved	Buccal membranes inflamed; gingivae hemorrhagic; fetor oris; local lymphadenopathy

TABLE 2 (CONCLUDED)

CONDITION	ORAL OR PHARYNGEAL LESIONS			DURATION (DAYS)	LABORATORY FINDINGS
	NUMBER	TYPE	LOCATION		
Herpangina	2-14; may be numerous	Vesicle, white-gray ulcer Areola	Fauces, anterior pillars, soft palate	3-6	"H" virus in feces and throat washings is pathogenic for infant mice Rise in antibody titer for "H" virus
Acute herpetic gingivostomatitis	Few	Vesicle, white-yellow ulcers Areola not usually described	Tongue, inner lips, buccal and sublingual mucosa Rarely soft palate, pharynx, larynx	10	Herpes virus from lesions causes keratoconjunctivitis on rabbit cornea Acidophilic intranuclear inclusion bodies in infected cornea Infected rabbits are subsequently immune to herpes virus

acteristic nature of herpangina which allowed for accurate clinical recognition long before adequate virus studies were available.

Extensive virus studies were carried out on the twenty-two patients in this series. While virus was isolated from the throat or anal swabs of several patients, the critical specimen for virus isolation proved to be frozen fecal material. Of the twenty-two cases studied, virus was recovered in nineteen. Virus isolation was accomplished in 86 per cent of the fecal specimens, from 59 per cent of the anal swabs, and 45 per cent of the throat swabs. Four immunologically distinct strains of virus were isolated which cause myositis, loss of muscle function, and death in suckling mice less than two weeks of age. These strains of virus have been classified as belonging to group A of the Coxsackie-type. A significant rise in type-specific antibody was demonstrated against homologous virus, that is, against the virus recovered from the patient studied. During convalescence neutralizing antibodies against homologous strains of virus were present in serum specimens from all of the patients studied, and in 70 per cent of the patients a rise in titer was demonstrated during clinical course.

It is of considerable interest that the patients reported in this study were uniformly free from signs of meningeal irritation. In one instance only did lumbar puncture seem warranted on the basis of clinical findings, in which case the spinal fluid obtained was completely normal, and on testing failed to give any evidence of the presence of virus. This observation is in striking contrast to that in patients with aseptic meningitis and paralytic or nonparalytic poliomyelitis from whom strains of Coxsackie virus were isolated, in that all of these apparently showed signs of meningeal irritation.

During the period of the investigations on herpangina, patients suffering from clinical poliomyelitis were followed at the Children's Hospital. Stool samplings were obtained from 131 patients, and none of these yielded virus characteristic of the Coxsackie group. Of fifty stool samplings from patients with diarrhea, only two yielded virus of the Coxsackie type. Stool specimens were obtained from patients with clinical poliomyelitis, diarrhea, and herpangina during the same period of time and according to the same time intervals.

In the studies on herpangina, the striking correlation between characteristic clinical manifestations and consistent investigative results in the laboratory suggests strongly an etiologic relationship between the Coxsackie group of viruses and this common, highly contagious summertime disease of children. On the basis of the study reported by these authors, the relationship between strains of Coxsackie-type virus and herpangina seems definite enough, and brings to mind again the interesting association of virus strains of this type with poliomyelitis. The isolation of Coxsackie-type virus from pharyngeal washings and anal swabs, and from a high percentage of stool specimens taken from patients suffering from this summertime malady of children suggests an epidemiologic pattern of considerable interest. A detailed description of the epidemiologic aspects of this disease is promised by the authors in a forthcoming paper, which will be awaited with interest.

This publication, as well as others which have appeared in the interim since Zahorsky's original description (1920) of herpangina as a clinical entity, pays tribute to Dr. Zahorsky's gift for accurate and complete description of clinical manifestations.

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News and Notes

The **American Board of Pediatrics** announces the following schedule of examinations for 1952:

Written examinations under local Monitors will be held on Friday, Jan. 11, 1952. This is the only written examination which will be given during 1952.

Oral examinations:

New York City, Feb. 1, 2, and 3, 1952.
St. Louis, Mo., April, 1952.
Washington, D. C., May 3, 4, and 5, 1952.
San Francisco, Calif., late June, 1952.
Chicago, Ill., October, 1952.
Boston, Mass., late November, 1952.

Dr. Joseph I. Linde of New Haven died Sept. 15, 1951. Dr. Linde was at one time clinical professor of pediatrics at Yale, where he became interested in and active in child health work. Since 1935 he has been health officer at New Haven. He was active in regional and national pediatric and health organizations and did much to bring the two into closer rapport.

Dr. Alex J. Steigman, professor of child health at the University of Louisville School of Medicine, is the recipient of a Grant-in-Aid from the National Foundation for Infantile Paralysis, Inc. The $23,635 grant is for the studies on experimental poliomyelitis.

Dr. Lyman T. Meiks has been appointed professor of pediatrics and chairman of the department of pediatrics at Indiana University School of Medicine, Indianapolis. Dr. Meiks succeeds Dr. Matthew Winters who has served as chairman for twenty years.

The **University of Minnesota** will present a continuation course in Child Psychiatry for general physicians and pediatricians Nov. 26 to Dec. 1, 1951. Dr. Reginald S. Lourie, director of the department of psychiatry, Children's Hospital, Washington, D. C., and Dr. J. Franklin Robinson, director of the Children's Service Center of Wyoming Valley, Wilkes-Barre, Pa., will be the visiting faculty members for the course. Dr. Reynold A. Jensen, associate professor, departments of psychiatry and pediatrics, University of Minnesota, is chairman for the course.

Notice has been received that the **III Pan American Congress of Pediatrics** and the **III South American Congress of Pediatrics** will be held concurrently rather than following one another at Montevideo, Uruguay, Dec. 2 to 8, 1951. There will be plenary and sectional meetings held at the new Clinics Hospital. A number of social activities have been planned as well as trips to summer resorts. The American Express Company, 65 Broadway, New York 6, has been appointed official transportation agency for those attending the Congress, and for pre- and post-Congress Tours.

The **National Foundation for Infantile Paralysis** announces the availability of a limited number of additional postdoctoral fellowships to candidates whose interests are research and teaching in medicine and the related biological and physical sciences. The purpose of these National Foundation fellowships is to increase the number of professional workers qualified to give leadership in the solution of basic and clinical research problems of poliomyelitis and other crippling diseases. The fellowships cover a period of from one to five years. Stipends to Fellows range from $3,600 to $7,000 a year, with marital and dependency status considered in determining individual awards. Institutions which accept Fellows receive additional compensation for expenses incurred in relation to their training programs. Eligibility requirements include United States citizenship (or the declared intention of becoming a citizen), sound health, and an M.D., Ph.D., or an equivalent degree. Selection of candidates is made by a Fellowship Committee composed of leaders in the fields of research and professional education. Complete information concerning qualifications and applications may be obtained from: Division of Professional Education, The National Foundation for Infantile Paralysis, 120 Broadway, New York 5, N. Y.

The **Section on Pediatrics of the American Medical Association** at the meeting held in June, 1951, decided to activate the **Jacobi Fund**, inactive since World War II.

The Fund had its inception at a meeting of the Section in 1929 for the purpose of

defraying the expenses of guest speakers, thereby promoting research and education in the field of pediatrics. It was named the Jacobi Fund to memorialize the name of the "father of American pediatrics," Abraham Jacobi of New York City. Jacobi, a former president of the American Medical Association, was the first chairman of the Section on Diseases of Children in 1880.

With no solicitation of funds for many years the principal of the Jacobi Fund now amounts to $5,532, invested in Government bonds, and the revenue is insufficient to carry out the purpose for which it was created. It is intended to stimulate interest in the Section meetings by inviting guest speakers as well as to reimburse our Director of the Scientific Exhibit and our Delegate to the House of Delegates of the American Medical Association. Both of these positions require a considerable amount of work, time, and travel expense and it is unreasonable to continue the practice of having the members who are elected to these positions bear all the travel and hotel expense necessary to carry out the duties of their officers.

It becomes necessary, therefore, to replenish the monies we have spent to reimburse distinguished guests and to expand our program. We are inviting all pediatricians to make a contribution of five, ten, or more dollars to the Fund. This is a deductable item on income tax returns. Please make checks payable to the Jacobi Fund and send to Hugh L. Dwyer, M.D., Custodian, 315 Nichols Road, Kansas City 2, Mo.

Book Reviews

Growth and Development of Children. E. H. Watson, M.D., and G. H. Lowrey, M.D., Chicago, 1951, Year Book Publishers, Inc., 260 pages. Price $5.75.

This text was started as a presentation of material for undergraduate students at Michigan, then expanded for the use of graduate students and residents, and finally into its present form. It is, as the authors state in the preface, "an accumulation from many sources" and "none of the data are original." It is somewhat of an encyclopedic collection of data referring to all phases of what is termed "growth and development," which has been shoved into the forefront of pediatrics by the stress that has been placed on the subject by the American Board of Pediatrics. Heredity, fetal growth, physical measurements, behavioral development, the development of the various organs and systems, metabolism and nutrition are included, as well as a final chapter on abnormal growth patterns. A bibliography is added to each chapter and the number of articles which have appeared on certain phases is amazing. The reviewer's chief criticism might be expressed by saying the text is uncritical, and that too much has been included to make it of value to the student. In physical measurements, for example, Stuart's, Simmon's, and even the obsolete Baldwin-Wood figures are included, and in graphic growth charts, those of Jackson, Olson-Highes, the Fels composite, and Wetzel grids. There is far more material in the book than the practicing pediatrician can possibly use, or need. For the "resident" taking the Board it would be quite bewildering if he attempted to master it all. For the teacher, or worker in the field, or as a book of reference, this collection in a single volume of all this material on growth and development scattered through the literature will be of great help.

Tuberculosis Among Children and Adults. J. Arthur Myers, M.D., Ph.D., Springfield, 1951, Charles C Thomas, Publisher, 894 pages. Price $12.50.

This book is most complete in its scope, and yet it is written in a concise style which has enabled the author to include all of the pertinent facts of present-day thinking on this important subject in a single volume. As the title suggests, those phases of the disease peculiar to the periods of infancy, early childhood, young adulthood, and later life are thoroughly discussed. Careful attention is given to consideration of the importance of detection of the first infection type of the disease among youth, to the diagnosis of the second infection type of the disease in youth, and to the treatment, prognosis, and prevention of pulmonary tuberculosis among

young adults. Certainly no one is better qualified to write upon these subjects than is the author who has devoted such a large part of his medical career to their investigation.

Recent trends in the therapeutic measures employed in the management of the disease are evaluated. Chapters are devoted to discussion of the roles of mechanical therapy, cavernostomy, extrapleural thoracoplasty, pulmonary resection, and of drugs in the treatment of pulmonary tuberculosis. Sections on diagnosis, mass surveys and the detection of tuberculosis, organization and projects, children and tuberculosis control, control of tuberculosis among students, and tuberculosis and war comprise the portion of the book dealing with the public health aspect of the disease. Some very interesting avenues of thought concerning the use of B.C.G. vaccine are provided in connection with the discussion of the toll of primary tuberculosis (tuberculous infection) and the effectiveness of control measures. The efficacy of other widely accepted means of reducing the mortality and morbidity rates of the disease is clearly presented.

The book should prove to be of great value to students of medicine in providing them with up-to-date knowledge of the many problems characteristic of pulmonary tuberculosis and, because of its wide scope, should serve as a useful reference for clinicians and those engaged in public health work.

D. M. S.

Your Deaf Child (A Guide for Parents). Helmer R. Myklebust, Ed.D., Springfield, Charles C Thomas, Publisher, 133 pages. Price $2.50.

This book written for parents is full of excellent detailed information on how to bring up the deaf child and at the same time can be used as a handbook for the normal child. One is impressed from beginning to end with how similar the training of the handicapped child is to the normal. Except in the field of speech the parents are urged to follow the ordinary training procedures.

Even in the field of lip reading and speech where the child is most handicapped suggestions are given the parents how best to assist their child. It is important to expose the deaf child to speech as early as possible and to utilize every bit of residual hearing he may have. As only a small proportion of children are totally deaf, hearing aids are often beneficial.

The attitude of parent toward handicapped child is discussed and a good common-sense point of view is taken, with real understanding of the problems which face the parent, such as blaming themselves, feeling frustrated, being ashamed, and the consequent reaction of spoiling, overprotection, or indifference.

Helpful information about organizations, schools, and books concerning the deaf child are found at the end of the volume.

In spite of the fact that there is nothing new or outstanding in this book it will prove a real aid to parents of the deaf child.

RUTH M. BAKWIN.

Schülernöte. M. Tramer, Basel, 1951, Benno Schwabe & Co., 160 pages. Price Fr. 9.80 (Swiss).

This is a monograph on the problems found in the school child. The physical and emotional problems encountered in the school child due to many conditions such as the small and the large child, retarded physical development for the age, stuttering, low intelligence, fatigue, nutritional disturbances, and the like are among the many discussed. The book is competely lacking in references to the work and studies of others, and the discussions of some subjects, as, for example, that of laterality and reading defects, which are common and create definite problems, are inadequately discussed.

Fussgymnastik mit Kindern. Martha Scharll, Stuttgart, 1951, Georg Thieme Verlag (Grune & Stratton, Inc., New York, agents for U.S.A.). Price DM 2.90.

This is a small pamphlet of twenty pages with twenty-six illustrations of exercises for the feet, for use with young children who need exercises and training for flat feet and pronation. It is a very practical and useful pamphlet which can be given parents as the illustrations are clear and to the point. Even a parent who cannot read the headings which are in German should be able to carry out the exercises from the illustrations. An excellent and useful little pamphlet.

Editor's Column

ANTIBIOTICS—WHITHER?

NO HONEST or self-respecting physician or surgeon, whether his practice be limited to pediatrics, geriatrics, or any other special field of medicine or surgery can help but feel a bit conscience stricken each time he prescribes or administers a sulfa drug or antibiotic after a hurried visit to the bedside of a patient or after a brief interview and examination in his office. Usually, however, he will find some comfort in the thought that in the great majority of his patients the illness for which he is prescribing will be self limited and that perhaps a significant proportion of these patients may actually benefit from the treatment. But even if he returns to find his patient improved, he will still wonder what part, if any, his prescription played in the improvement. He can then take solace only in the idea that at least he "played it safe" even though he still does not know just what he was treating. Or, perhaps he will find comfort in the thought that everybody else is doing the same thing. Unfortunately many physicians feel impelled to prescribe these agents only because they are expected to do so, for if they do not, their patients would discharge them in favor of others who would.

What is the reason for the present widespread and unbridled use of antimicrobial agents? It has its origin, of course, in the lifesaving potentialities of these agents. No one can deny the fact that the sulfonamides and antibiotics are highly effective in the treatment of serious infections with many organisms and that they have markedly reduced the mortality from such infections. They have also been responsible for numerous recoveries in such diseases as bacterial endocarditis and in many of the meningitides which prior to the advent of these drugs were almost always fatal.

However, it is equally obvious to any one who has used these drugs that they are far from universally effective. In general, there is a direct correlation between the sensitivity of the organism to the antimicrobial agent in vitro and its clinical effectiveness against the diseases caused by these organisms. But the sensitivity of the organism is not the only determining factor. The number and accessibility of the organisms to the drugs, the local presence of conditions or substances which interfere with their action, the emergence of resistant variants of the original pathogens or of the naturally resistant organisms which multiply and assume pathogenic significance—these, and perhaps other factors that are less well understood, may vitiate the beneficial effects of the sulfonamides and antibiotics even when used in the treatment of infections which are caused by apparently susceptible organisms.

It may also be noted, in passing, that the in vitro tests for sensitivity, which are usually considered to be the main support for the intelligent and proper

use of antibiotics, are far from infallible. Such tests may yield results that are difficult to interpret since they may vary within extremely wide limits depending on the details of the methods that are used.

In actual practice, however, antimicrobial agents are used without too much consideration of these factors. Only the most obvious manifestations of severe toxic reactions that are readily and directly attributable to these agents will deter some practitioners from prescribing them even for mild and self-limited infections. Moreover, even the most casual survey of the uses of these agents, either in the home or in hospital practice, will reveal that only a relatively insignificant part of the total amount of sulfonamides and antibiotics that are dispensed today are prescribed for the treatment of susceptible infections. By far the greatest proportion of these drugs are given for "borderline" indications and for uses that are considered to be "prophylactic." Such uses have, in most instances, only the remotest or the most indirect relation to any proved efficacy of these agents in the conditions for which they are prescribed.

The difficulties of obtaining properly controlled and decisive information in clinical cases have led many workers to make broad and unwarranted generalizations and extensions from inadequate and uncontrolled observations. Much of the enthusiasm for the unbridled use of these and other important agents has been generated by the wishful thinking of our popular science writers and publicists who are always there to blow up pretty bubbles. Even our most oustanding scientists and those who have made the greatest tangible contributions to the subjects have often added unwittingly to the confusion. In "dreaming" about their discoveries, as they are wont to do under the scientific heading of "discussion," the most careful scientists often suggest extensions and uses that go far beyond the data that are presented. But their suggestions are taken up as proved facts by uncritical readers. Needless to say the modern high-powered sales and advertising forces of many of the manufacterers in the highly competitive pharmaceutical industry have contributed more than their share to the confusion in their attempts to sell their wares.

It is likely, however, that the abuse of these important and lifesaving remedies will continue indefinitely, unless a change occurs in the attitude of both the medical profession and the public. Such a change in attitude has already occurred with respect to the sulfonamide drugs. At least two major factors have combined to decrease the popularity of the sulfonamides in favor of penicillin and the other antibiotics that subsequently became available; these are the relative decline in the effectiveness of the sulfonamides and the increase in the number of patients who developed serious untoward reactions from them or have become sensitive to them. In the gonococcal and some hemolytic streptococcal infections, the decline in effectiveness of sulfonamide drugs appeared to be a direct result of the appearance and rapid increase of sulfonamide-resistant strains. This, in turn, could be attributed to the widespread and almost universal use of these agents, both therapeutically and prophylactically, which presumably permitted resistant strains to spread while eliminating or significant-

ly decreasing the relative numbers of sensitive strains.

It is now becoming evident that similar factors are already operating with respect to the antibiotic agents. When penicillin was first introduced it was certainly the most effective and least toxic of any anti-infectious agent that had ever been known. That is probably still the case. However, the occurrence of increasing numbers of cases of sensitivity reactions to penicillin in its various forms and the relative increase in the proportion of cases of bacterial endocarditis and of staphylococcal infections due to penicillin-resistant organisms may be cited as evidence heralding the eventual decline in the value and effectiveness of this, the first major antibiotic. The alarming frequency with which streptomycin-resistant tubercle bacilli are being encountered in patients in whom active tuberculosis is discovered for the first time and who have never received any of this antibiotic suggests very strongly that streptomycin, the second major antibiotic, may also soon lose its effectiveness against the very disease for which it has found its greatest use.

There are also similar portents of a decline in efficacy and increase in toxicity of the "broad spectrum" antibiotics, which in many areas in this country already have surpassed their predecessors in the extent to which they are used. The use of multiple agents, as recommended by some workers on the basis of limited evidence from isolated cases or diseases, may temporarily increase the effectiveness of treatment in such cases. But there are also some indications that some combinations of agents may actually be less effective than the individual ones for certain infections. This use of multiple agents, nevertheless, has already become widespread not only for therapy, but also in prophylaxis. Such usage may, at best, reduce or postpone the decline in efficacy of the antibiotics. At the worst, it may hasten the evolution and spread of microbial agents resistant to all of the antibiotics that are now in wide use.

It may be pertinent to ask: Are we in medicine, like our counterparts in industry, exhausting our most valuable resources at too rapid a rate? Are we, perhaps, depending too much on the ingenuity of our scientists and industrialists to keep constantly ahead of this decline? Only time will tell. In the meantime, is it not prudent to think more in terms of how these valuable antimicrobial agents can be used most effectively rather than most widely?

M. F.

PROGRESS IN THE FIELD OF ADOLESCENCE

SEVERAL months ago an article on the growth of boys during adolescence by Dr. J. Roswell Gallagher, published in the July, 1950, issue of the *Yale Journal of Biology and Medicine,* came to the attention of the editor. It was such a sane and practical discussion based on Dr. Gallagher's many years of study and observation of adolescent boys, that the thought immediately arose that this was an article which should be of great help to the pediatrician in practice. The article was read and discussed by members of the Editorial Board of the JOURNAL, with the result that it was decided to break a precedent of twenty

years and republish it in its entirety in the JOURNAL (p. 532) rather than in an abstract form. Permission was given by Dr. Gallagher and the Editor of the *Yale Journal*, to whom we express our thanks for allowing the article to become more generally available to pediatricians.

Shortly after this decision was made it was learned that Dr. Gallagher was to head a new Division of Adolescence at the Children's Medical Center in Boston, and had been appointed assistant professor of Child Health in the Harvard School of Public Health. Dr. Gallagher was for many years physician to the Phillips Academy, Andover, where he developed what was regarded by many as the outstanding school health service in the country. He and his associates at Andover have made a number of important contributions in the field of adolescence and the activities of adolescent boys. This fall the Atlantic-Little Brown press has published his new book, *Understanding Your Son's Adolescence*, which was the outgrowth of several contributions to the *Atlantic Monthly* which attracted wide attention.

The opening of this new Division of Adolescence at the Children's Medical Center at Boston in September of this year marks a distinct advance in the development of pediatrics. It has been considered a part of the field of pediatrics by pediatric education for a number of years, as the period of adolescence is a part of the continuing process of growth of the individual from birth to maturity. We know of a number of children's hospitals and pediatric departments which have discussed the idea of a division of adolescence, but have been unable to carry out the idea because of administrative difficulties and interdepartmental relations. This pioneer effort, or experiment, on the part of the Harvard School will be watched with tremendous interest. It will undoubtedly bring to light many problems and difficulties to be solved, and the experience at the Children's Medical Center at Boston will be of invaluable aid to other departments and institutions in integrating the adolescent period more closely into the field of pediatrics than exists at present. They are fortunate in having a man of Dr. Gallagher's caliber and experience to head the experiment.